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Edited by

LEWIS STEPHEN PILCHER, M.D., LL.D.

in conjunction with

FRANK E. ADAIR, M.D.

INTERNATIONAL CONTRIBUTIONS TO THE STUDY OF CANCER
IN HONOR OF

JAMES EWING

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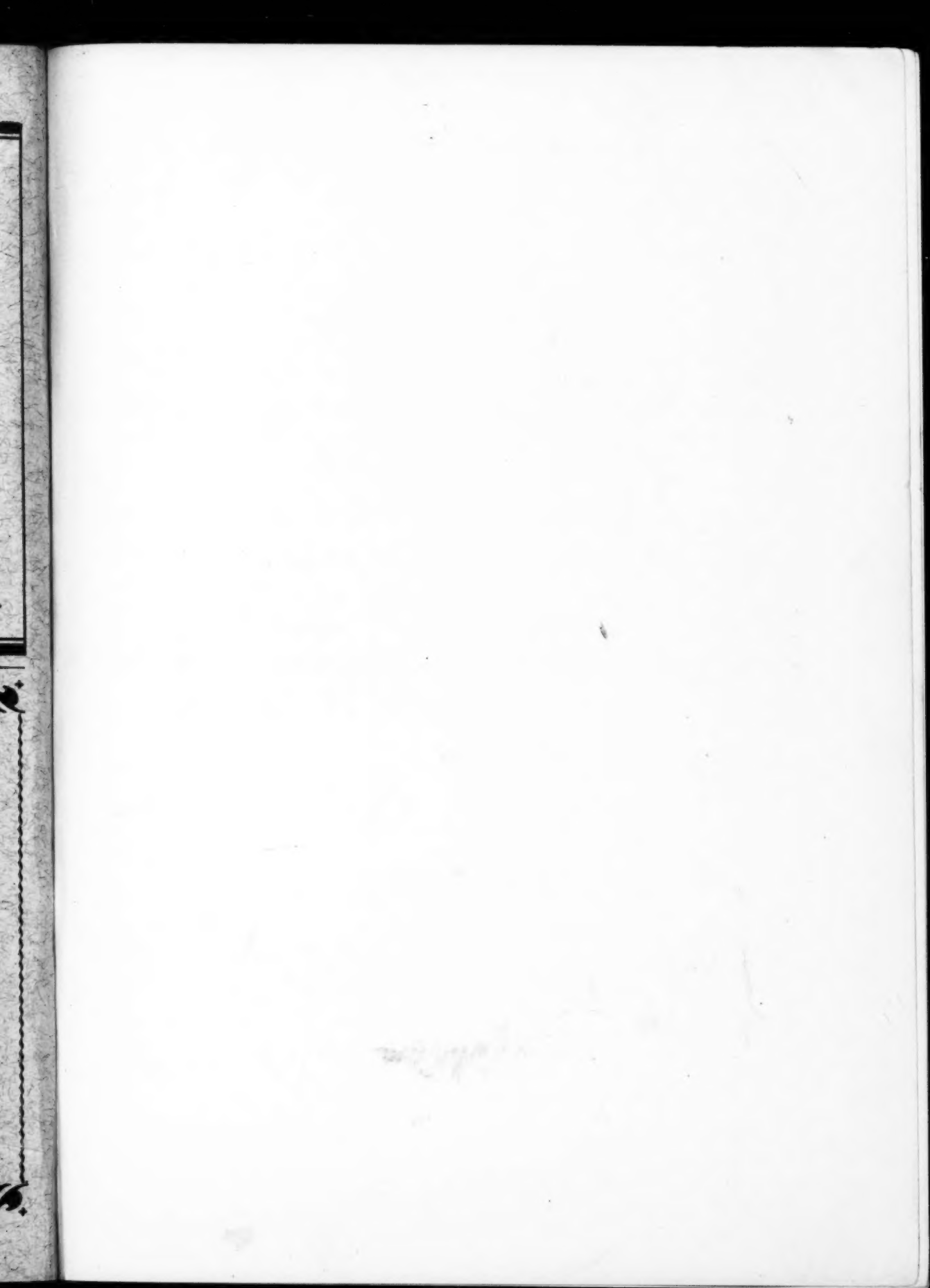
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ARRANGED IN FOUR PARTS

PART I. CANCER IN ITS GENERAL RELATIONS

PART II. CANCER RESEARCH

PART III. REGIONAL CANCER

PART IV. RADIUM AND RÖNTGEN RAY THERAPY

WITH CONTRIBUTIONS FROM
THE FOLLOWING COUNTRIES

AMERICA—BELGIUM—CANADA—ENGLAND—FRANCE—GERMANY
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AN APPRECIATION

THIS volume, in honor of James Ewing, serves the twofold purpose of a tribute to one of the leading active pathologists of the world who is likewise the foremost American investigator of the entire group of neoplastic diseases, and of a contribution of great value to the subject of cancer. Did the conditions of a homage volume permit the dedicatee to present a paper the value of the contribution would be still further enhanced.

In a note on the development of the homage volume published in the *Bulletin of the American Association of University Professors** Professor Morley formulates a code of ethics for a *Festschrift* as follows:

1. The dedicatee should be recognized as an international leader in his field of research.
2. He should be an eminent trainer of scholars, as well as himself an eminent scholar.
3. These conditions being fulfilled, the recipient would naturally have attained, as the French say, a certain age—about sixty-five, the retiring age in many colleges, which is a natural milestone, though it has not often been observed.
4. The contributors should be former pupils and colleagues and workers in the same specific field; friends they should be, but not admitted only because they are friends.
5. The volume should be as carefully edited as any professional journal, and no article admitted which does not reach that standard.

Every one of these conditions is fully met in this volume. Carefully edited by Doctor Adair, it is a tribute by colleagues and workers in the special field of cancer to Professor James Ewing, an eminent scholar, an eminent trainer of scholars, an international leader in pathology, especially in the field of the cancerous diseases upon the attainment of his sixty-fourth birthday, December 25, 1930.

After his graduation as Bachelor of Arts from Amherst College in 1888, and as Doctor of Medicine from Columbia University in 1891, Doctor Ewing enjoyed for seven or eight years the admirable opportunities for training and experience in pathology furnished by Doctor Prudden's laboratory at the College of Physicians and Surgeons, Columbia University, where he served successively as Tutor, Fellow and Instructor before assuming the duties of the Professorship of Pathology at the Medical School of Cornell University in New York, to which he was called in 1899—a chair which he has occupied with remarkable success both as teacher and investigator for thirty-one years.

Not the least of the memorable services to medical education and the advancement of pathology and public health in this country of that great pioneer of modern pathology in America, T. Mitchell Prudden, was the inspiration,

* Vol. xv, No. 4, p. 293, April, 1929.

training and direction which he imparted to an able and devoted group of pupils and assistants during his incumbency of the Chair of Pathology at Columbia University for three decades from 1879 to 1909. The most eminent disciple of this school to carry on and extend the work of the master is the one to whom this volume is dedicated.

While this volume especially signalizes the value of Doctor Ewing's studies in the large and important field of malignant new growths there is scarcely a domain in pathology which he has not cultivated, be it morphological, chemical, clinical or experimental. In this brief introduction to a volume devoted exclusively to cancer no attempt can be made to enumerate the contributions made by Doctor Ewing to pathology in over one hundred and fifty papers, monographs and textbooks. In his early studies, especially those upon the blood, he revealed that interest and competence in cytology which have remained a distinguished mark of his researches for the last quarter of a century upon tumors, and are strikingly exemplified in his important textbook "Neoplastic Diseases," first issued in 1919 and now in its third edition.

Doctor Ewing early recognized the vast and growing significance of the problem of cancer, or as he has properly and effectively taught us to say, "the *problems* of the cancerous or neoplastic diseases"; and he likewise early discerned the importance of attacking these problems by combined pathological and clinical studies, indeed from every promising angle of approach. The width of range represented by the writers and papers in this volume dedicated to a pathologist typify the far-flung interests and the breadth of view of Doctor Ewing himself in all aspects of the subject of malignant diseases.

Not the least of Doctor Ewing's services is that while his pronouncements in the diagnosis of cancer are authoritative, he has exerted a wholesome critical and restraining influence upon hasty generalizations and undue optimism in the interpretation of pathological, etiological and clinical investigations and work. That such measured and considered statements are especially important at the present time is evident when one bears in mind that cancer is today the outstanding problem in medicine and public health; that it threatens the ascendancy of all other causes of death; that its study engages the attention of workers in all fields of medicine and surgery and does not escape the attention, even of biologists remote from medicine; that increase of opportunities for such study makes an especially strong appeal for more generous financial support; and that education both of the medical profession and of the public is the most essential part of the present active campaign for the prevention and cure of cancer.

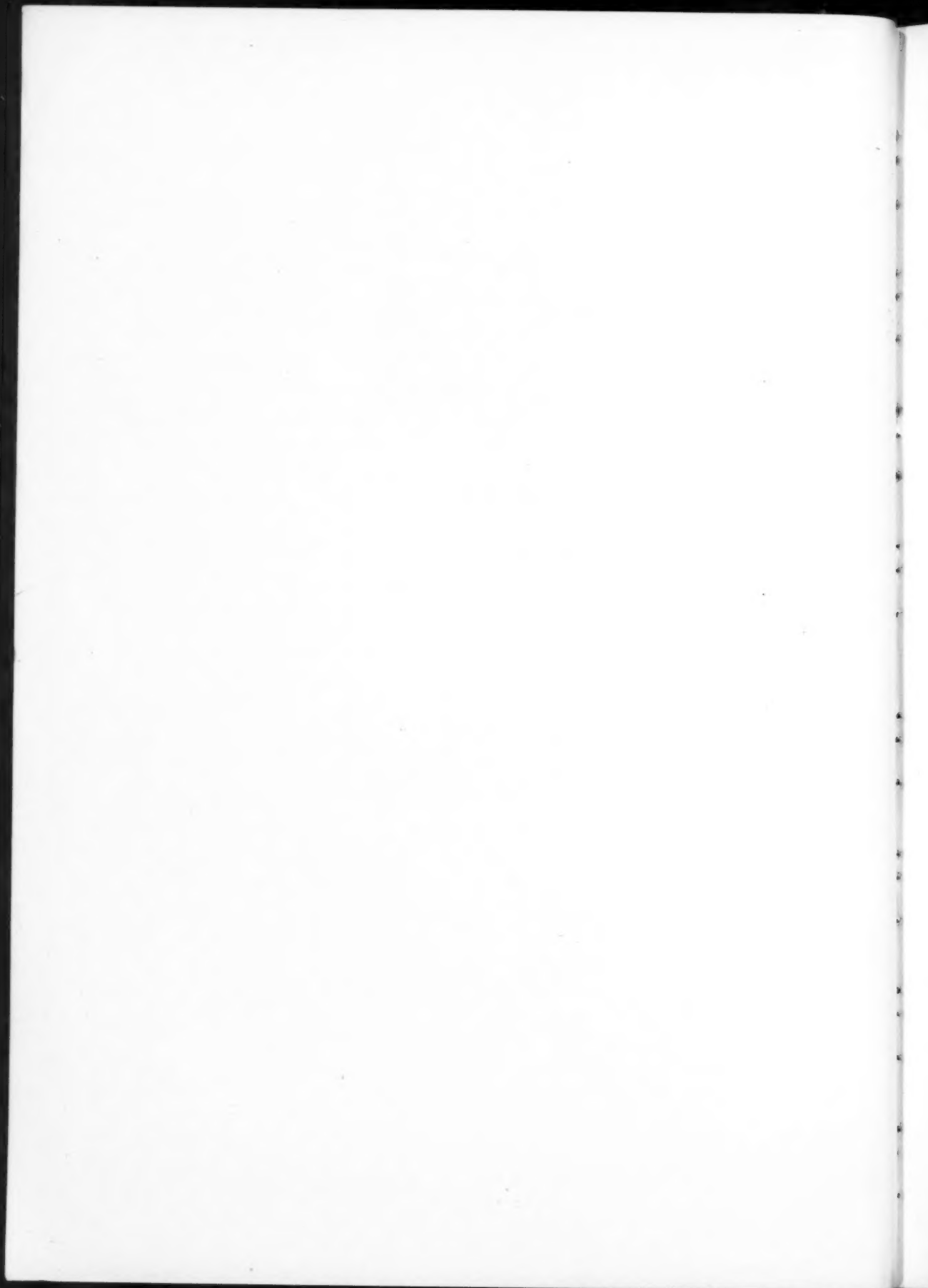
In the failure to unlock the ultimate secret of the causation of cancer one is likely to overlook the fact that there are few diseases concerning which more additions to our knowledge have been made in the last half century than in the group of cancerous diseases. The so-called "cancer campaign" is abundantly justified by the strikingly improved results of treatment by radical surgery or by radiotherapy attendant upon early diagnosis and prompt

AN APPRECIATION

treatment. Nor is there any reason to be hopeless regarding a deeper insight into the causation of these diseases.

As a fellow pathologist, in behalf of the contributors to this volume as well as of all students, of the problems here considered, and of a host of pupils, colleagues, friends and admirers, I venture to congratulate Doctor Ewing upon the sixty-fourth anniversary of his birth, to felicitate him upon his many years of fruitful and beneficent activities as teacher, investigator and writer, and to wish him many years of happiness and of continued influence and service in the advancement of useful knowledge.

WILLIAM H. WELCH,
Johns Hopkins University, Baltimore, Md.



FOREWORD

THE purpose of this volume is to honor a man who has devoted the largest part of his life and professional career to the investigation of that mystery-disease, cancer. No tribute to such a man could be more appropriate than a *Festschrift* on the subject which lies nearest his heart. During the past decade, cancer has made most alarming progress in civilized countries; and in America since 1928 it is exceeded in death-rate only by heart disease and pneumonia. The problems of cancer are so numerous, so widely divergent and so baffling that it seems timely to assemble the most recent knowledge on the various subjects of cancer research, pathology, surgery and radiotherapy from the scattered clinics and laboratories of Europe and America.

When this suggestion was made to many of the international authorities, they, although burdened by the responsibilities and demands of their work, responded with hearty enthusiasm. Accompanying their scientific contributions were many notes which expressed the authors' admiration, respect and affection for Doctor Ewing. As an example we shall quote the letter of Professor W. Lazarus-Barlow:

My dear Ewing:

A Festival number is something unusual and so I have no scruples about prefacing the contribution I am proud to make to it, with a few personal words.

I should like to assure you of the great affection and respect with which you are regarded by myself and, I am convinced, all pathologists in Great Britain. You will not, I am sure, take it wrongly, when I say that we feel there is something in your method of approaching subjects and in your mental attitude which appeals in the strongest degree to our Old World conservatism and caution. Truth is so elusive and has so many facets that repeated verification of observations, care in drawing deductions and, above all, caution in publication seem to be essential if we are not to be snowed under by an avalanche of ill-digested material. These qualities you possess in a very high degree and on that account, amongst others, you are exercising a profoundly beneficial effect upon medical literature. I hope that you will long live to exercise that influence and that you will accept my contribution as a small token of my great regard.

Yours very sincerely
W. S. LAZARUS-BARLOW

West Mersea, Essex, England
May 1st, 1930

As a man Ewing is simple in habits and tastes; sincere; intensely loyal; helpful to colleagues; possessing a subtle humor; a lover of competitive sports; tactful in the handling of men and opposing forces; scientifically resourceful and imaginative; optimistic always; idealistic in his belief in men; indulgent to a fault; having an unusual sense of fairness; scientifically aggressive and persistent; one who welcomes and encourages new avenues of approach to problems; a tireless worker; a severe but constructive critic;

FRANK E. ADAIR

discriminating in his estimate of scientific contributions; a stimulating teacher; a forceful lecturer; an indefatigable contributor to scientific movements; a scholar beloved by students and colleagues; a physician of the highest ideals.

The study which he made of radiated tissue is the basis of his strong support of radiotherapy. Radiology and radiotherapy in America owe a great debt to Ewing.

The original members of the Bone Sarcoma Registry of the American College of Surgeons freely admit that Ewing's enthusiastic support kept this monumental work from perishing by neglect. His broad clinical experience and diagnostic acumen have made him a unique figure among American pathologists.

Probably his greatest scientific contribution is his book "Neoplastic Diseases." It is the standard reference and textbook of the world on that subject. The magnitude of assembling all the known facts about neoplastic diseases and subjecting them to a critical and orderly analysis would have daunted any man of ordinary courage. The need was great, the opportunity available, and so for ten years Ewing worked with zealous ardor, holidays, nights, week-ends, stopping for minutes only to fight the paroxysms of tic douloureux. And so did Ewing persevere and work. Today his "Neoplastic Diseases" is a monument to his systematic intellect and his genius.

The relationship of Ewing to the Memorial Hospital can best be expressed in the words of Emerson—"Every institution is but the lengthened shadow of some man." Doctor Ewing is the Memorial Hospital.

We wish to express our great appreciation to Dr. Lewis S. Pilcher, Editor of the ANNALS OF SURGERY, who so warmly welcomed our suggestion of this volume; and who has been so indulgent and helpful in the editorial work.

Our gratitude goes out to the J. B. Lippincott Company who found us utterly despondent before certain difficulties of our undertaking, and whose suggestion made this opus possible.

FRANK E. ADAIR,
Memorial Hospital, New York, N. Y.

December, 1930.

BIOGRAPHIC DATA

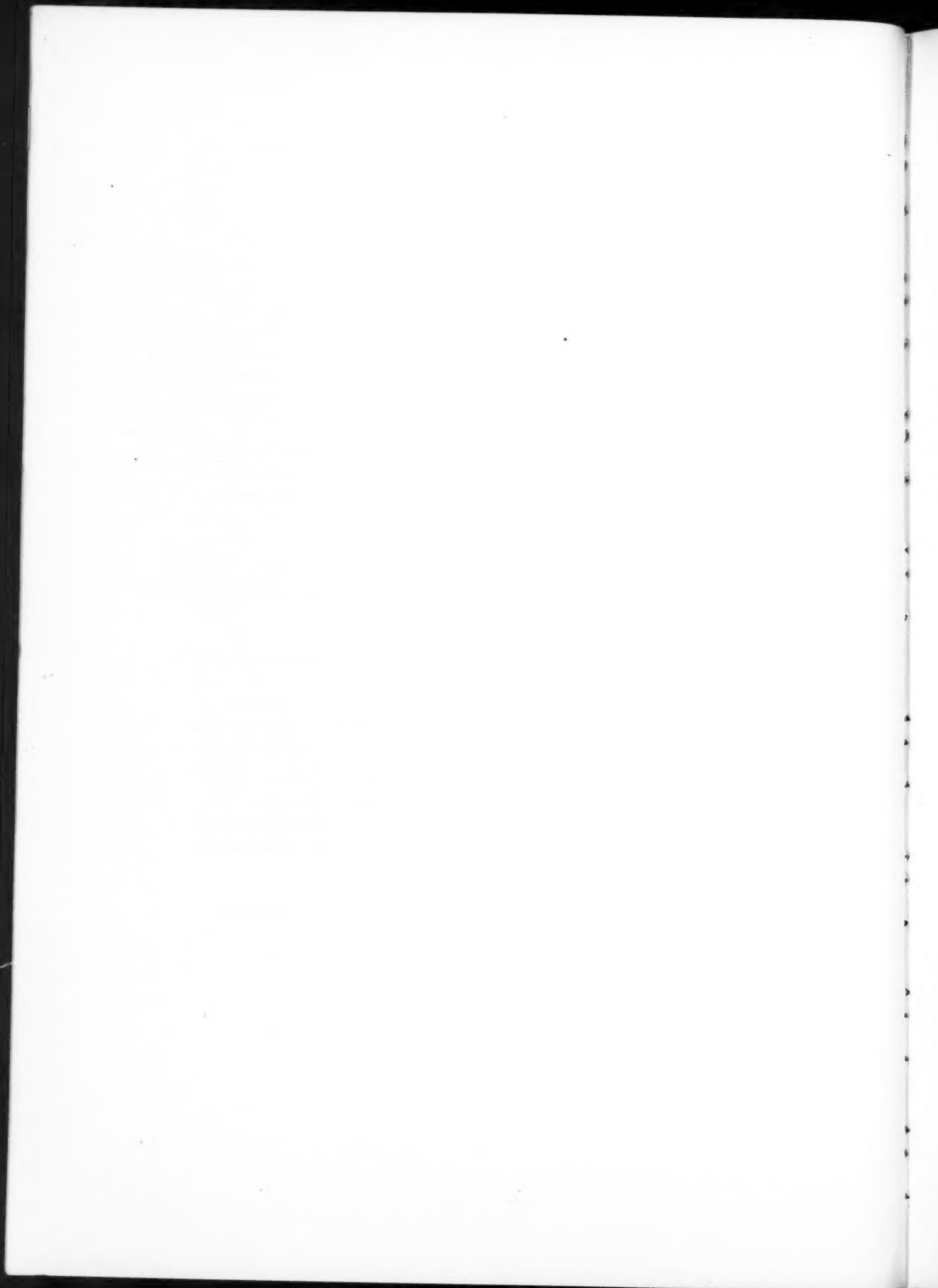
RECORD OF JAMES EWING, M.D.

Biographical Data: Born, Pittsburgh, Pa., December 25, 1866; Bachelor of Arts, Amherst, 1888; Master of Arts, Amherst, 1891; Doctor of Medicine, Columbia, 1891; Doctor of Science, Honorary, Pittsburgh, 1912; Amherst, 1922.

Professional Positions held: Tutor Histology, Columbia, 1893-1897; Clark Fellow, Columbia, 1896-1899; Instructor Clinical Pathology, Columbia, 1897-1898; Professor of Pathology, Cornell, 1899 to date.

Contract Surgeon in charge of Museum work in Washington, World War.

Society Memberships: Amer. Assoc. of Path. and Bacter. (Pres. 1906); Association of Amer. Physicians; Soc. of Exp. Biol. and Med. (Pres. 1912); Amer. Assoc. for Control of Cancer; Amer. Assoc. for Cancer Research, (Pres. 1907); Fellow, Amer. Med. Association; Harvey Society (Pres. 1908); Fellow, New York Academy of Medicine; Amer. Roentgen Ray Society; Amer. Med. Museums Society; Amer. Assoc. Pathologists and Bacteriologists; N. Y. Pathological Society; Amer. Radiological Society.



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JAMES EWING

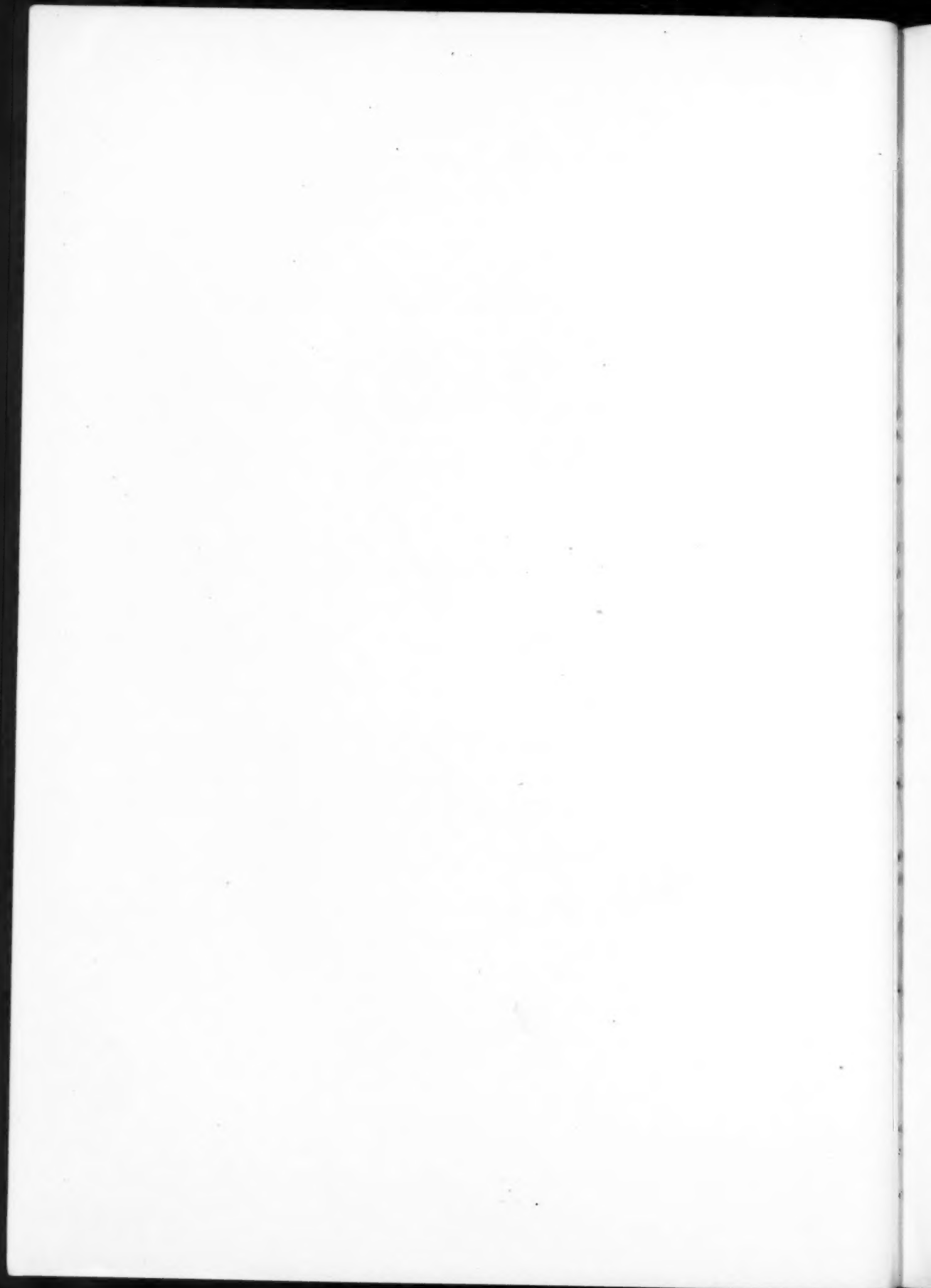
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I

CANCER IN ITS GENERAL RELATIONS

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Lecturer in Surgery, Kings College Hospital and Surgeon to Kings College Hospital.
"Natural Law in Pathological Growth."
- CLARENCE C. LITTLE, Sc.D. Bar Harbor, Maine
Director of the American Society for the Control of Cancer.
"A Brief Analysis of the Present Status of the Cancer Problem from an Administrative Point of View."
- WILLIAM J. MAYO, M.D. Rochester, Minn.
Chief of the Mayo Clinic.
"Susceptibility to Cancer."
- W. CRAMER, M.D. London, England
Director of the Imperial Cancer Research Fund.
"Resistance and Susceptibility to Cancer."
- H. T. DEELMAN, M.D. Groningen, Holland
Professor of Pathology, University of Groningen.
"Hereditry and Cancer. A Statistical Study."
- WILLY MEYER, M.D. New York, N. Y.
Consulting Surgeon to the Lenox Hill and Post Graduate Hospitals.
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- MAUD SLYE Chicago, Ill.
Director of the Cancer Laboratory of the Otho. S. A. Sprague Memorial Institute and the University of Chicago.
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Consulting Statistician, Prudential Insurance Company of America.
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- F. BLUMENTHAL, M.D. Berlin, Germany
Director of the Cancer Institute of University of Berlin.
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- WILLIAM B. COLEY, M.D. New York, N. Y.
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INTERNATIONAL CONTRIBUTIONS

TO THE

STUDY OF CANCER

IN HONOR OF

JAMES EWING

NATURAL LAW IN PATHOLOGICAL GROWTH

BY SIR G. LENTHAL CHEATLE, F.R.C.S.

OF LONDON, ENG.

INTRODUCTION.—The definite control over the formation of pathological epithelial new growths is a remarkable feature of their existence. This control is universal and more marked in the benign epithelial new formations than in the malignant types. In carcinoma it is not so universal nor so marked except in certain examples. Let me draw particular attention to the benign epithelial new formations. In all benign epithelial new growths the nature of control they exhibit is identical with the normal conditions of physiological new formations. The control, however, is imperfect. The tissues and seats of new formations may be localized to parts where the process of new formation of a similar character is occurring normally elsewhere in the same glands. For example, the same epithelial and connective tissues that are actively forming in a breast at the age of puberty may at one part or more than one part be forming a type of fibroadenoma. In this tumor new ducts and acini may develop in far greater proportion than in the parts that are normal. These new ducts and acini may be normal in size, shape and appearance while others are irregular in these respects. At other times new and nearly normal formations may occur when the rest of the glands are at rest.

However great are the variations in the normal activities of tissues in which the new formations occur or the varieties of their seats of origin in them, there is exhibited a control of development and structure that is akin to the physiological process. The new formations resemble in structure the physiological growth that occurs in the respective glands and tissues in which they grow.

Another fact should be borne in mind in considering natural law and pathological growth. And it concerns the normal functions that govern the uses of a cell apart from the laws that govern the structure of which it is a part.

The normal uses and functions of all varieties of cells have a marked influence upon morphological appearances of tissues when they become pathological. Take, for example, a fibrous connective tissue cell and three varieties of epithelial cells. Desquamation takes no normal part in the function of a fibrous connective tissue cell and it exhibits desquamation in none of its pathological lesions.

The normal functions of an epidermic cell belonging to the horny layer involve its being constantly shed and renewed. In pathological lesions of the skin the desquamating effects of these epithelial cells alone are seen in dermoid cysts when the walls of which contain no hair follicles nor sebaceous glands.

The normal function of an epithelial cell of the breast entails its being shed for the purposes of elaborating the secretion of milk. The normal shedding of epithelial cells for the purpose of elaborating secretion is also taking place in the prostate and sebaceous glands. In the pathology of breast, sebaceous and prostate glands cystic states depend upon the shedding of desquamating epithelium. Cysts thus formed are consequently very common in these glands.

The function of an epithelial cell in the intestine, kidney, adrenal glands and liver does not include its being shed for the purposes of elaborating either their secretions or excretions as may be. Cysts due to epithelial hyperplasia and neoplasia are uncommon in these viscera principally because epithelial desquamation plays no part of their normal function.

For thirty years I have studied the breast and other glands by cutting them into whole microscopical sections. The study particularly included normal breasts from birth onwards and all forms of diseases that affect the mammary gland. The accessibility and frequency of disease of the breast always made it appeal to me as being an ideal structure to study. The study of a diseased or normal gland always appeared to me to be inefficient unless the whole of it were presented to the observer in microscopical sections of the entire gland. Many important points have been discovered by means of this process. By not having limited myself to the study of breasts alone I can see opportunities for fresh discoveries in other glands and tissues of the body if they are examined by the same method. This method of study proves that although the organs and tissues of the body differ from each other in function and structure there are the same pathological processes affecting them all. The chief differences between them are ordained by their differences in function and structure; for example, a gland containing ducts and acini differs from that which contains only acini or alveoli by the additional changes that occur in the ducts.

The breast and thyroid glands undergo precisely similar changes of adenomatous tumors, cystic formations and malignant diseases. The chief differences between the pathological changes occurring in them are caused by the presence of ducts in the breast. Mr. R. S. Wale and I have recently pointed out that the pathological changes in breasts and prostate glands are

very similar; both, for example, pass through all the changes of a disease Schimmelbusch first called attention to as existing in the breast.*

The pathological changes in the gastro-intestinal mucous membrane differ from those of the breast, thyroid and prostate glands only by the differences in structure and function. The epithelial elements in all of them undergo similar desquamative epithelial hyperplasia and benign and malignant epithelial neoplasia. The similarity between the pathological changes in breasts and intestinal epithelium are striking. For example, an adenoma of the intestine resembles an adenoma that has formed in a duct of the breast. Because a duct of the breast is so small in calibre that a growing tumor within it induces its dilatation it has given rise to the erroneous, misleading nomenclature of "intracystic adenoma." Adenoma of the colon occurs in a tube of so large a calibre that it cannot be dilated sufficiently to lead the observer into the false position of believing it to be an "intracystic" tumor.

It is interesting to realize how common it is for most epithelium to form papillomata and to see how the differences in function and structure of the epithelium composing them lead to changes which differ from each other in the different glands and tissues only in those respects. For example, first let me take the papillomata that arise in the epithelium of the ducts in the breast. The function of the epithelium of the breast is to secrete and increase the area of glandular secreting surfaces on different occasions during life. As a rule the papillomata of the breast begin by an ingrowth of two or more stalks of pericanalicular connective tissue taking in with them the elastica of the duct wall. The stalks are covered by two layers of epithelium, giving rise to a multiradicular papilloma. These stalks branch and their branches may grow without showing an early tendency to anastomose with each other or with those of neighboring stalks. On the other hand two stunted papillomata may lean toward each other immediately upon their formation and anastomose before any branch has appeared, giving rise to a small cavity or acinus lined by epithelium which at once loses its columnar shape and becomes cuboidal. The cavities that are formed by the anastomoses of neighboring branches of a more developed papilloma are larger and more irregular, but still exhibit the same changes of columnar cells into those which are cuboidal in shape. These changes may be so complete that I have examples of papillomata that contain complete arrangements of ducts lined by columnar epithelium and acini lined by cuboidal epithelium. These are the altered papillomata that have given rise to the misleading term of "intracystic adenomata." In some of these tumors carcinoma has begun. The differences in morphological appearance between them and the papillomata and adenomata of the colon depend only upon their difference in structure and function.

The papillomata growing from the pelvis of the kidney, the urinary bladder, the epidermis and those arising from the ducts of the breast and the colon are chiefly due to the differences in structure and of function. The

* *The British Journal of Surgery*, April, 1930.

functions of the epithelium of the pelvis of the kidney, urinary bladder and epidermis are chiefly those of providing a covering or lining surface. The functions of breast epithelium are a great deal more complicated and at puberty and lactation it has to form new glandular elements.

It is remarkable that a wart of the skin consists only of epidermic cells and contains no glandular elements or hair follicles of the skin that exist in such profusion over its whole distribution. A wart of the skin is a pathological process that selects and affects the epidermic cells only. The function of the epithelial cells of the epidermis is to cover surfaces.

While new glandular formation is in progress in normal breasts at puberty a fibroadenoma may occur that consists of precisely the same tissues that are undergoing physiological activity elsewhere in the gland. There can be no doubt that the same influences controlling the normal physiological state are in a disturbed degree also controlling the formation of the tumor. The same type of fibroadenoma occurs in mazoplasia when the same tissues of the gland are active when they should be at rest. The same tissues that are active at puberty are also active in mazoplasia in the breasts of non-pregnant women at thirty-five or forty. The activity of mazoplasia may be distributed equally over the whole breast, but it is not so regular as it is at puberty. New ducts and acini and pericanalicular and periacinous connective tissue hyperplasia occur in both conditions.

Pure adenomata also are examples of new breast formation in tumors in which there is only a slight new connective tissue constituent.

The remarkable intracanalicular fibroadenoma, the connective tissue element of which is provided by the subepithelial connective tissue that exists between the epithelial cells and the elastica, is a striking example of a tumor in which beautiful new breast elements are formed. I have described these tumors as occurring in the breasts of women who are generally older than those in whom occur the pericanalicular and periacinous connective tissue fibroadenomata of puberty. As the subepithelial tissue of these tumors bulges into the duct in sessile shapes it is covered by the duct epithelium. From the surface of the tumor secondary papillomata may arise. But what is to me the most interesting thing about these tumors is that the surface epithelium often dips down into the underlying connective tissue and forms clusters of beautifully formed, lusty acini of which any young breast might well be proud. They are joined to the surface by a cellular tube of epithelial cells to form a duct. One of these tumors containing these beautiful glandular formations occurred in an intracanalicular tumor of a woman aged fifty-two years. All sorts of speculations arise from this fact into which I do not intend to enter. Without speculation it can be said with obvious truth that the new glandular formations in the normal development of a breast and in breasts of puberty and pregnancy are subject to normal physiological control. The new glandular formations I have just described in the different kinds of fibroadenomata, however normal they may be in arrangement and appearance, cannot be considered as being normal. Yet they are under some power-

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ful, deliberate control which is not far removed from a purely physiological and functional one. All these tumors appear to be benign at their periods of conception. The fibroadenomata and adenomata remain benign throughout their histories in the vast majority of examples, and should they become malignant it is their connective tissue elements which become anaplastic and either morphologically appear to be sarcomatous or actually develop metastatic growths.

Papillomata, on the other hand, are not so consistent in their maintenance of the benign state and their careers are definitely and commonly associated with the termination in carcinoma. The benign tumors upon which I have been speaking are only less under control than the normal processes to which I have compared them, but they are under a control closely resembling the normal one in many essential features.

It is a question whether these benign tumors should be so definitely delimited from each other as they are in the textbooks and in the present outlook with which they are regarded. I believe these tumors are bound together etiologically by their attempts to reproduce normal structures and functions. A striking feature common to these benign tumors is their capacity of being multiple in origin.

It is not so common to discover either sarcoma or carcinoma arising from multicentric sources of origin. The source of these diseases is usually limited to one part of a tissue or gland in the body. When carcinoma occurs in a gland its source is usually limited to one part only.

I have five unusual specimens of breast carcinoma which bear on this point. The whole of the glandular epithelium in all the ducts and acini in all of these specimens is in a state of malignant and highly anaplastic neoplasia. In four of the specimens carcinoma has occurred in one area only. In the remaining one there is regression of the neoplasia and no invasion by epithelial cells into outside tissues.

It is unfortunate that the only test that can be applied to establish the condition of what is called carcinoma is that of epithelial cellular invasion. I am convinced that the biological change of malignancy begins before it manifests itself by infiltrative growth into outside tissues. Directly this manifestation occurs the state is recognizable as being one of carcinoma. The primary tumor from which the infiltrating cells are derived is contained within normal boundaries and can be seen in early specimens of breast carcinoma. The epithelial cellular invasion is only a secondary matter, so far as the process of carcinoma be concerned, although it is of such fatal importance concerning the future of a patient.

The carcinomata that may affect the thyroid, adrenal and thymus glands often cannot be distinguished morphologically or functionally from the normal structure of these glands. Thus even carcinoma can afford the same evidence as the benign tumors I have been alluding to, in that it also may assume methods of growth and function that are present in the normal

physiological states. The fact of there being evidence of physiological control in benign and carcinomatous tumors, however imperfect it may be compared to the perfect control that exists in the development and growth of normal structures, naturally leads to the question of whether it throws any light upon the etiology of either benign or carcinomatous tumors. The failure of being able to adduce decisive experimental evidence compels the answer to be completely speculative and unsatisfactory and further compels all who are interested in the subject to maintain a mind open to all the known and unknown theories that wrack and may wrack respectively all consideration upon the matter. A step toward its solution would be attained if carcinoma always could be traced, passing gradually from a benign state into the malignant one. The process would indicate a progressive transformation in which the appearance of each stage depended upon the stage by which it has been immediately preceded.

There is, in fact, an indication of a progressive process of this kind in the remarkable disease described as Schimmelbusch's disease of the breast in which there is a sequence of events that ends in carcinoma in about 20 per cent. of all cases of carcinoma of the breast. The disease as I translate it begins as a desquamative epithelial hyperplasia which causes cysts. This stage of the disease begins in the late twenty and early thirty years of life and may not pass into the next stage. When it passes on, the next event occurs in the late thirty and early forty years of life and consists of a radical change in the biology of epithelial growth which becomes neoplastic, all the epithelial cells of which are viable and are contained within normal but distended boundaries. The formation of papillomata is a marked feature of this stage. The change from desquamative epithelial hyperplasia into epithelial neoplasia can be seen in all stages of accomplishment. The disease may stop at this stage. When it passes into carcinoma, as it may do, the passage occurs in the late forty and early fifty years of life. In such specimens all three stages of the transition can be traced definitely. On first consideration the process appears to be a definite gradual transition from innocency into malignancy by means of three definite stages which occupy about twenty or thirty years to mature. During the transit the papillomatous growths may exhibit so marked a control and ordination of development that they contain actual duct and acinous structures.

Here again five questions arise: (1) Whether the march of events is only a definite consecutive process? (2) Whether the sequence of events is induced by the continuous action of the same factors? (3) Whether the advent of each event is induced by a completely different factor? (4) Whether all the stages of transformation are due to a disturbed intrinsic physiological process? And (5) whether an extrinsic factor can induce pathological changes that exhibit more than suspicion of physiological control? The last question is the only one that space allows me to discuss.

I will begin by drawing attention to a fibroma that Dr. A. M. Begg dis-

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covered in a fowl.* The tumor looked innocent and was so hard in consistence that he was unable to pound it into a pulp for purposes of filtration. He transplanted this tumor and during its subsequent transplantations it became softer and metastasis occurred. The tumor also became filterable and the filtrate reproduced highly malignant tumors upon inoculation. This tumor may have been either malignant from the beginning of its career or subsequent passages may have made it become so, or some other factor may have entered the arena and created the change in the biological state of the tumor cells.

Fantastic as the notion may first appear, there may be no such thing as a benign tumor, but really all may be malignant and their careers may be interrupted or stopped at any stage.

The signs of physiological control in benign and malignant tumors does not lend any support to the theory that, in consequence, tumors cannot be due to the introduction of an outside agent. The examples of the introduction of outside agents, such as spermatozoon, mechanical irritation and alteration in diet, leading to physiological growth in various examples are too obvious to need recapitulation.

Turning to this question of the genesis of carcinoma, it is one in which I have a completely open, not to say vacant, mind. Yet there are one or two examples of epithelial neoplasia that end in carcinoma into the genesis of which the introduction of an outside agent as a causal factor cannot help creeping into one's mind.

When only one whole duct of a breast and all its branches is picked out as the site for the growth of epithelial neoplasia, its site is so localized that it looks like the accidental incidence or the selection by design of an outside causative factor. This remarkable distribution of epithelial neoplasia occurs in certain examples of papillomata of the breast.

There is another instance which affords the same suggestion of an outside agent being in coöperation with the development of an epithelial neoplasia. The underlying breast of Paget's disease of the nipple develops epithelial neoplasia in many of its parts, sometimes papillomata, sometimes epithelial neoplasia that morphologically appears to be malignant but still confined within normal boundaries, and at other times carcinoma itself.

Paget's disease of the nipple is an affection of the epidermis only of the nipple which extends to the surrounding epidermis of the skin. This fact has been proved by Dr. R. J. Ludford in one recent case of mine. This is what he says:

"I have examined this case of Sir Lenthal Cheate's as completely as possible from a cytological standpoint. The cytological examination proves that Paget's disease of the nipple is a purely epidermic condition, the cells of which could not have been derived from the mammary carcinoma cells of the underlying tumor.

* *British Journal of Experimental Pathology*, vol. x, p. 322, 1929.

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"During the course of the cytological examination the cells of the carcinoma in the breast and those of Paget's disease of the nipple have been investigated: (1) The chromophility of the cytoplasm (three methods). (2) The cell lipoids, including mitochondria (two methods). (3) The Golgi bodies. (4) The chromatin, as demonstrated by Feulgen's reaction for thymus-nucleic acid.

"All stages of transition of epidermic cells were seen to be taking place in the same microscopic field from normal cells onwards. There are no malignant cells from the breast tumor in the epidermis in the area of Paget's disease."

The chief and most interesting point about Paget's disease of the nipple is always—so far as my experience goes—associated with one of the forms of epithelial neoplasia I have already mentioned. The occurrence and variety of these forms suggest the introduction of an outside agent. Paget's disease of the nipple and the carcinoma of the underlying breast is the strongest example I know that acts as a support for the notion that the introduction of an outside agent can be the cause of biological changes that end in carcinoma.

Finally, the above observations indicate the existence of a systemic control over the formation and genesis of benign and malignant tumors. Is the nature of this control merely one of hereditary tendencies upon the affected cells, or are they influenced by a disturbance in the normal action of internal secretions? There is considerable experimental evidence to show that epithelial and connective tissue hyperplasia may be induced by over-activity of the corpus luteum. This action of the corpus luteum is capable of being prolonged by hormones in the anterior lobe of the pituitary gland. The relation of these hormones to diseases of the breast can be—for the moment—only inferred.

The chief notion pervading this article was drawn particular attention to by Dr. C. W. Nicholson in his classical little book upon "The Nature of Tumor Formation." In his book Doctor Nicholson generously points out that we were thinking about and publishing the same notion at the same time.

THE PRESENT STATUS OF THE CANCER PROBLEM

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ALL SORTS of agencies, individual and institutional, have for years been interested in the investigation of the complex of processes, dealing with research, education, and therapeutics which we may describe as the cancer problem.

Although few, if any, very startling discoveries have been recorded, the sum total of gradual progress has been considerable. It certainly seems to justify us in hoping that within the next few decades there will be still further advances in our knowledge of the nature of the processes which constitute the uncontrolled growth of the tissue of human beings—known as cancer. It is also to be hoped that wherever and whenever possible the efforts of research workers, public health officers, medical men, and the public-minded lay citizen will be highly coöperative. This is extremely desirable because as a result of the complexity of the problem and the great diversity in type of the various agents investigating it, there is a real need for the development of consolidated and unified points of view and for agencies to make the application of such points of view possible.

With this in mind it may be well from time to time to focus our attention on a general analysis of the main features of the problem as a whole with a view to clarifying the situation and to correlating the various efforts which are being made.

Any one of a number of methods of describing, grouping and classifying the different items which together constitute the total problem might be used. Since, however, obstacles to progress are so common in cancer work, it may be well to base our analysis on a consideration of certain of the lines of work which may have grown up as a natural result of the focus of interest on the part of many investigators and clinicians. Lines of work originating without preconceived plan represent, in a way, an indication of the actual terrain—the high and low points, the fertile and sterile areas in the problem. We may fairly inquire as to the general fields of work in one or more of which progress must be made if order is to be brought out of chaos and the organization of the problem be made possible.

There are at least four great fields of the work in which new advances are necessary. More satisfactory and complete methods of classifying and of differentiating between the various types and degrees of cancerous growth will have to be established. The best possible methods of treatment must, of course, constantly be subjected to close scrutiny with a view to improvement and refinement and to the development of new lines of attack. Besides

this there is the immensely important work of attempting to decrease the incidence of cancer by education of the layman in the value of prompt report, early treatment, and the avoidance of causes of needless and obvious irritation. Finally as a fourth problem there is the cause or causes of uncontrolled cancerous growth. The nature of this phase of the subject is such that it obviously demands and will continue to require long periods of painstaking research.

It may seem that it should be easy to make progress in all these lines, but such is not actually the case. Let us see whether we can visualize the factors entering into the situation and acting as obstacles.

In attempting to discover the cause or causes of cancer we have been greatly handicapped by our continued procedure of considering this phase of the problem as one of medical nature. The fact that some of the ordinary theories or tests might prove applicable to cancer has never been entirely lost sight of. Repeated and always unsuccessful efforts to discover a micro-organism which should prove to be the chief causative agent of cancer have been made. In a somewhat similar fashion those who first tried to determine the rôle of heredity in the production of cancer made the great mistake of attempting to prove or to disprove not only the major question of its inheritance, but the number of Mendelian factors involved, by studies of human pedigrees. Evidence of that indirect sort, involving, as it does, much of the quality of rumor, imperfect records, and hearsay, lacks the accuracy which is essential in experimental scientific work. It can be used in a general statistical way to considerable advantage but neither its collection nor its interpretation is a matter primarily medical in nature.

Even when the long-delayed shift from the study of second-hand human data to first-hand experiments with animals in the laboratory was made, the further mistake was made of ignoring essential methods of genetic control. Stock animals obtained from a single dealer, or caught in a single locality are not sufficiently uniform genetically to be used for genetic experiments on cancer. Many large experiments are, however, recorded in scientific publications where even less than the above mentioned is attempted. As a result contradictory and inconclusive findings have delayed our advances and have served to complicate the question of heredity still further than was necessary.

To mention another confusing factor, only recently have we reached a point where we can state first, that biologically there are many forms of cancer; second, that each type thoroughly investigated with adequately controlled material seems to depend in part at least upon constitutional factors which are inherited; third, that the exact type of inheritance is complex and very likely is different in different types of cancer. These statements are not hard to understand if one keeps in mind the fact that many different types of tissue are involved in the various sorts of cancer and that agents which result in abnormal growth of one sort of tissue may quite possibly leave another type entirely unaffected.

Reasoning from analogy and from the human data on record, one may

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conclude that studies of heredity may well prove to be one of the most successful means of analyzing the cause or causes of cancer; but that because there are many types of cancer biologically different, as a practical force in preventing its dissemination in man by control and application to individual cases, heredity will not prove to be extremely important.

This does not mean, however, that careful records of every possible individual and family should not be kept and that in special cases heredity may not become a factor worthy of consideration. The efforts now being made in most western countries to gather more complete vital statistics are, therefore, in every way commendable. By more accurate and more extensive vital statistics we are able to detect at as early a date as possible any correlations existing between cancer and age, race, sex, occupation, and a whole grist of abnormal or pathological conditions of anatomy or of physiology. Furthermore, such studies give us the only reliable basis for determining the actual increase or decrease of the incidence of cancer of any given type. Improved methods of diagnosis, a higher percentage of hospitalization, the extension of the average period of life, and more and better autopsies are all factors that may contribute to *recognition* of cancer. This in turn may give the appearance of an actual *increase* in cancer incidence, although it may not have increased in the least.

In the broad field of detection and classification of cancer, human material as it comes to the clinic, hospital or pathologist, can be used advantageously.

Successful efforts to develop a method of yearly diagnosis by which the presence of cancer can be detected at much earlier stages than are at present possible would be a great advance in saving life. Rumors of the discovery of such a test are frequently recurrent. None, however, has as yet been formally accepted by the medical profession.

The classification of cancer by the physiological manifestation of its vigor and virulence, as shown by its rate of growth, frequency of metastasis and invasion of normal tissues, also needs much further study. It is entirely probable that the successful growth of human cancer cells *in vitro* will be followed by advances in all these fields of investigation.

The questions of genetics, of diagnosis and of classification together form a group which may be said to depend very largely on the extent of our knowledge of the nature of the internal environment of the individual in the laboratory or clinic, as the case may be. Recent studies in experimental morphology and embryology are beginning to give us a preliminary picture of the complex relationships which exist inside the body of a mammal. We are still far from being in a position to understand the situation, but a beginning has been made. As a result the importance of the various physiological elements which contribute to the development and control of such processes as growth is becoming more and more clearly recognized.

In matters of treatment we meet for the first time the trained medical worker in direct contact with the cancer problem. The use of surgery,

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radium and X-rays—forming as it does the trio of generally recognized treatments—is well known to all.

Any technic of removal of a cancer, whether by the actual cutting of surgery or the burning by X-rays or radium, has the unavoidable danger of being incomplete even when practised by a highly skilful person. To that is added, in the case of radium and X-rays, the danger of injuring the normal tissue or even of stimulating abnormal growth in regions surrounding the destroyed area. This does not mean that surgery, radium or X-rays do not effect cures in certain cases. In fact it has been repeatedly shown that they may. It does mean that the experimental efforts to improve methods of measuring the dosage of X-rays and radium and of applying them should be continued and increased until all sources of error which can be eliminated have been done away with. Further work with electro-surgery will also have to be done. In this connection a very natural and sometimes desirable conservatism of the medical profession which makes it slow to accept any new technical methods may have to be combated.

To aid in the practical solution of this question the organization of clinical centres where the best possible diagnosis and treatment of cancer can be had is needed at or near all large centres of population. As a forerunner of this the studies of hospital and radium facilities now being made by the American Society for the Control of Cancer are significant. So also is the work of the American College of Surgeons which has taken up the task of outlining what it feels to be adequate hospital facilities and of inspecting hospital units to determine whether they meet the requirements.

Undoubtedly the various geographic units, whether they be states, counties, or municipalities, will need individual study and treatment. The work of the American Society for the Control of Cancer has already progressed far enough to show that any general method applied without discrimination would not be successful in every case. Another source of weakness is that there are surprisingly few hospitals in the United States in which anything resembling an adequate "follow-up" method as regards cancer patients is attempted. This condition must be corrected and an attitude of patient research which recognizes the essential nature of long-continued records must be developed. It is hard to make investigators interested in collecting data for later generations to use, but it must be done in the case of such a late-developing condition as cancer.

In all these problems the need of larger numbers of better trained medical men is paramount. Because of many reasons, among which the difficult and discouraging nature of cancer itself is undoubtedly one, the medical schools and active medical profession give much too little attention to training would-be or young doctors in the problem of cancer. Instead of recognizing the challenge offered by cancer as being an outstanding menace about which pathetically little is known and for the combating of which the utmost coöperation is needed, the medical profession fights shy of grappling with the problem and looks for easier foes to conquer. This attitude will have to

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be corrected. The spread of popular interest in cancer, coupled with a marked decrease in ignorant fear and superstition concerning it, will undoubtedly in the near future result in a popular demand by the laity for better equipped medical men to cope with the situation. Then, if not before, medical schools and the medical profession as a whole will take the long overdue steps toward more up-to-date and extensive training of their personnel.

In matters involving education of the public, care should always be exercised not to make overenthusiastic claims nor to arouse false hopes. Public educational campaigns always should be preceded by a survey of clinical and hospital facilities, and the form which the educational campaign should take in any locality should depend very largely on what such a survey reveals.

The public is eager for information about cancer. It is gullible and quickly aroused. Caution and patience are necessary in dealing with laymen when cancer is the topic under consideration. For this reason it is especially unfortunate that the ethics of the so-called profession of journalism should be, in many cases, as poorly developed as they are. The newspapers have, in numerous instances, been the means of undoing much of the good which might have accrued from carefully worked-out campaigns of education. By the publication of quack cancer "cures" and the premature, unintelligent and overenthusiastic publicity on many "new treatments" the press has built up unfounded hopes to be followed by a bad mental reaction in thousands and tens of thousands of people. Headlines that use the "selling" phrases of sensationalism; articles that are based on an almost negligible foundation of scientific knowledge are among their sins. The better journals are not so much to blame. They have tried honestly to paint a true picture of the situation and have been and are willing to be cautious and reasonable. Unfortunately there are, however, enough popular second-rate or third-rate sheets to discredit and handicap efforts at public education in the field of cancer work.

Much can and will be done by teaching the public to avoid unnecessary and possibly dangerous irritants and to report suspicious signs of potential cancer at the earliest possible date to some reputable physician or at some accredited hospital.

Taken as a whole it would seem that those interested in the cancer problem have cause for encouragement. The increase in biological knowledge has begun to give us a picture of what controls and shapes the course of growth. The support of state and Federal departments of health which can serve as the means of collecting and studying a superior type of vital statistics is increasing. The greater urbanization which exists all over the country gives a chance for great and able centres of clinical work and hospitalization of cancer cases. The wider spread of education makes the public less difficult to approach in any campaign of information. Finally the interest in public health and the point of view of the preventive medicine "attitude" are reforming and revitalizing our national life in such a way as to make possible a steady increase in the investigation of cancer and in the speed of our progress toward its eventual control.

SUSCEPTIBILITY TO CANCER

By WILLIAM J. MAYO, M.D.

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THE impressive statistics showing that cancer in the human species is increasing are at least open to question. Reliable computations show that a greater number of persons live to reach middle age or longer, when cancer is more common.

In countries that compile trustworthy statistics the incidence of cancer is approximately in the same ratio to population and sex, but there is considerable divergence in the different organs and tissues involved. In this country, about 30 per cent. of deaths from cancer among women is due to cancer of the breast and genitalia. In men the incidence in the genitalia is very low. On the basis of cancer of the generative organs, therefore, one would expect the total incidence of cancer in men to be considerably lower than in women, but the percentage is approximately the same, because in men the organs common to both sexes, such as the stomach and the organs of the urinary system, are more often affected by cancer than in women, and this increased frequency equalizes the high percentage of instances in which the breasts and uterus are the seat of cancer in women.

One of the few known facts about cancer is its relation to later life. In women the senile changes which take place in the breasts and uterus at the menopause are a factor in bringing about cell changes which invite cancer. The genitalia in men undergo no such sudden and profound senile changes; inasmuch as the testis is the primitive organ of procreation from which the ovary is derived, it has a protective heredity behind it.

It is worth while occasionally to go back and take account of stock, so to speak, to see what we really know about cancer that has stood the test of time.

We have thought of cancer so much in relation to the human being that we have not always kept clearly in mind that every living thing may suffer from an analogous disease. The late Dr. Erwin F. Smith, working in the government laboratories in Washington, found that cancer in plants had the essential characteristics of cancer in man, and he noted the relation of these types of plant tumors to certain bacteria which he believed to be the cause either of such cancers or of irritation in susceptible plants which resulted in those changes in cells which were responsible for the tumors.

The development of cancer in the lower animals has received a greater amount of study than cancer in plants, and is fairly well understood. The disease in the lower animals, again, exhibits the same general characteristics as in man: that is, cell changes, growth to the limit of obtaining blood supply, and transplantability in the same animal through metastatic processes, with which we are only too familiar.

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Cancer does not appear in sound tissues. Investigation of the various theories of the causation of cancer shows that the one provocative agent which remains unchallenged is chronic irritation. In all lands, among all peoples, we see this one causative influence in the ascendant. In China, among those who shave their heads with a dull and rough-edged razor, cancer of the scalp is common, but does not occur among those who do not shave the scalp. The Chinese men eat at the first table, when the rice is hot, throwing it with some force by means of chopsticks into the mouth and pharynx, and not infrequently they suffer from cancer of the pharynx and the beginning of the œsophagus. The women, who eat at the second table, when the rice is cold, seldom have the disease. In Australia the sharp-edged sand in the desert portion of the country, blown by the hot wind, so frequently produces cancers of the skin of the face that such cancers are called the "Australian disease." In certain parts of India and the Philippines, where the betel nut wrapped in its leaf with lime is chewed, cancer of the mucous membrane of the cheek is still common. Among smokers, cancer of the lip sometimes develops, less commonly since heat-conducting clay pipes are no longer used. Cancer of the gums and about the teeth is less common now that by modern methods of dentistry irritating stumps and roots may be removed. Cancer of the breast occurs largely among civilized women. In those countries in which the breasts are allowed to be exposed, that is, are not compressed or irritated by covering, it is rare. In the mountain regions of Kashmir, India, where the people carry braziers filled with hot coals strapped onto the lower part of the abdomen, cancer just above the pubis is common.

With improvements in construction of buildings and change in fuel, there are no longer many chimneys which require cleaning, so that chimney-sweep's cancer of the groin is less common, but we still see an occasional cutaneous epithelioma on the shins of railroad engineers and firemen whose legs have been exposed during years to the intense heat of the engine fire-box.

I have merely touched on these few outstanding examples of cancer of visible parts of the body about which there is little dispute. As to cancer of the interior of the body we have less definite proof, but cancerous gall-bladders usually contain stones, and that ulcer of the stomach may be responsible for cancer of the stomach is admitted by all, although there are great differences of opinion as to its frequency. Hurst has given statistics to show that in about 20 per cent. of cases of ulcer of the stomach, cancer may be expected. In our own experience, while the percentage in which the histologic examination of excised cancers of the stomach for evidence of preceding ulcer varies in different series of cases, the development of gastric cancer on some type of demonstrable precancerous disease such as ulcer is present in more than 25 per cent.

Cancer of the stomach in men constitutes a third of the total number of cancers in all parts of the body. The cause of the greater frequency of cancer of the stomach among men has not been solved. The men of the

*Learned
reliability?*

races that do not confine themselves to civilized customs are less often affected by cancer of the stomach. Do hot drinks change the gastric epithelium, or does food in large quantities wear out its secretory function so as to produce premature changes in the gastric epithelium? Cancer of the small intestine is rare as compared with cancer of the stomach, large intestine and rectum, which have a short heredity as compared with the primitive small intestine, and this may be a factor.

When we try to estimate the exact relationship of sources of chronic irritation to cancer, there are various explanations. Certain observers believe that the site of chronic irritation, unprotected by normal epithelium, permits the entrance of an outside agent, perhaps a microorganism, but if so, why should the metastatic process always show the histopathologic characteristics of the original lesion? A metastatic process in the liver from a cancer of the gastro-intestinal tract shows, not cancer of the liver, but a secondary cancer of the gastro-intestinal epithelium in the liver.

A possible explanation is that when the tissues have been subjected to a long-continued insult, the reparative processes are exhausted and, instead of healthy cells, less mature cells are thrown into the breach of continuity until finally embryonic cells are used to replace the normal epithelium.

New revelations would make it appear that cancer may be the result of agencies acting from within the body due to biochemical dysfunction affecting the life history of embryonic cells. In any event, it may be assumed that the agents which act on the cell to produce malignancy become an inseparable constituent of the cell, as metastasis takes place only by the transplantation of the malignant cell itself.

Individuals vary in their susceptibility to the cause or causes of cancer, whatever they may be. In no other way can we explain why 90 per cent. of persons do not have cancer, and why 10 per cent. of them die from it. It is as logical to accept the hypothesis that the 90 per cent. of persons have greater resistance to cancer than the 10 per cent., as to attempt to force an explanation of why only 10 per cent. come in contact with hypothetic causative agents. If the patient's susceptibility to the disease is the significant factor in the development of cancer, the site of the growth would be determined by the tissue or organ subjected to the insult of a precancerous lesion, and the grade of malignancy and the metastatic possibilities by the susceptibility of the body as a whole. Perhaps the reason cancer usually appears after middle life is that the cells of the body have lost the reparative power of youth, have a lessened immunity, and thereby have become more vulnerable.

Certain sources of chronic irritation seem to have greater potentiality to produce malignant disease than others, such as unrefined tar, which seems to possess more than ordinary powers of precancerous irritation for susceptible animals.

The local response of the tissue subjected to chronic irritation apparently is influenced by general systemic factors which may either accelerate or delay the development of cancer. Murray's work leads to the inference that there

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are variations in the resistance or, conversely, in the susceptibility of individual mice to cancer from tar painting. Slye found that by breeding strains of mice in which the disease developed most readily, the susceptibility of these strains could be increased enormously, so that mice would be born with the disease. By mating mice that were not so readily susceptible to cancer, strains could be developed in which cancer could not be produced and to which cancer could not be transferred.

The malignant cell has a remarkable resemblance to the rapidly growing embryonic cells of the chorionic villi (Langhans' cells). The stroma of a cancerous growth is the measure of nature's resistance. The greater the amount of stroma and the less the proportion of cells, the slower the growth. Wilson, MacCarty, and Broders have enlightened us greatly with regard to the histologic character of the cell in relation to malignancy. Wilson was able, twenty-five years ago, to develop an original polychrome methyl blue stain for frozen sections which gave good differential coloration of the various elements of the cell, thus making possible an immediate microscopic diagnosis. MacCarty called attention to the significant fact that the greater the proportion of the nucleus and the less the differentiation of the cell cytoplasm, the more rapid the growth of cells; that an excess of the nucleolar element is associated with the type of rapid growth and invasion which is clinically malignant. Broders, in a careful clinicopathologic study of the relative amounts of cell differentiation in a tumor, pointed out that the more nearly the cancer cell approaches normal, the less the malignancy, and was able to develop an index of malignancy. Bowing found from experience with radium and X-ray that the more severe grades of cancer, Grades 3 and 4 of Broders' classification, may sometimes be made to take on the more favorable aspects of the cancers of Grades 1 and 2, with definite slowing of the process, so that sometimes such a lesion primarily inoperable may become operable.

The assumption has always been that the more severe grades of cancer are due to a more potent cause. I hardly need point out that these newer revelations throw some doubt on so ready an explanation. It is equally, if not more, probable that the more severe forms of cancer and the development of cancer in certain tissues are due to increased susceptibility.

The foregoing studies logically lead to the idea of increasing individual resistance to the disease and its ultimate prevention. Science has been able to develop soil changers in smallpox, diphtheria and tetanus. Why not in cancer? Because of natural immunity to the disease relatively only a small proportion of the total population is susceptible to scarlet fever. With the Dick test the degree of natural immunity of the individual to scarlet fever can be determined, and if it is not sufficient to protect from the disease, it can be increased to normal by serum. Why not in cancer? Perhaps the development of cancer as well as its degree of malignancy is attributable to the diminished activity of immunizing processes rather than to the nature of the activating agent.

RESISTANCE AND SUSCEPTIBILITY TO CANCER

By W. CRAMER, M.D.

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FROM THE IMPERIAL CANCER RESEARCH FUND

WHEN the experimental production of cancer by painting with tar or other carcinogenic agents had been developed as a laboratory method, so as to yield positive results in practically 100 per cent. of the tar-painted animals, it was demonstrated beyond doubt that cancer was at its inception a local disease which arose in a limited area of cells subjected to chronic irritation. It was natural that at first the attention of workers in this field was riveted upon the *production* of cancer and that most of the work was designed so as to induce cancer as rapidly as possible and in the greatest number of animals subjected to the experiments. This could be obtained by applying tar as frequently as possible consistent with the survival of the animals, by applying tar to a relatively large area of skin and by continuing the application of tar to each animal until a tar cancer appeared.

Experimental Demonstration of Resistance.—If, however, the opposite device is adopted (that is to say, if tar is applied to as small an area of skin for a limited period of time and with a frequency just sufficient to induce cancer with a fair degree of regularity in a certain percentage of the experimental animals), quantitative differences are revealed in the reaction of different individual animals to tar painting, which are of considerable significance. The results of a typical experiment of this kind will make the meaning clear. In this experiment 100 female mice aged from three to six months were subjected to the repeated application of an actively carcinogenic tar preparation. The preparation used is one which had been kindly placed at our disposal by Professor Passey. A drop of tar was applied twice weekly to the epilated skin between the shoulder-blades. This was continued for four months. After that period no further tar was applied to any of the mice, which were allowed to complete the natural span of their lives. As soon as warty growths appeared, they were entered on charts and when a growth was considered to have become malignant, it was removed by operation and the diagnosis verified by microscopic examination. One object of this procedure was to determine the onset of malignancy as accurately as possible. It was unavoidable that in a few cases tar tumors were excised which on microscopic examination proved to be of doubtful malignancy. There was a massive hyperplasia and downgrowth of the epithelium, but no clear evidence of infiltrative growth. Such tumors, which were, fortunately, only five in number, are not classed among the tar cancers. In addition to the mice which developed tar cancers of the skin, there were those which developed papillomata which remained in that state until the death of the animal. A third group of negative mice remained without any growth whatever until their

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death. When the mice died any growth present on the skin was examined microscopically and search was made for the presence of metastases or of neoplasms on other parts of the animals. In such an experiment one obtained therefore three groups of animals, which will be called: (1) The cancer group; (2) the papilloma group; (3) the negative group. These will now be discussed separately.

(1) *The Cancer Group*.—Table I and Fig. 1 give the number of mice which developed tar cancer in each month reckoned from the beginning of tarring (December, 1927). The total number of mice with tar cancer is fifty-one. The first two tumors appeared at the end of the fourth month just at the end of the course of tarring. One of these two tumors appeared at once as a malignant growth, and, although excised as soon as it had been noticed, metastases developed in the axillary glands one month later. The number of tar cancers showed a rapid increase and reached a maximum in the sixth and seventh months. This was followed by an equally rapid decline in the following months. The last tar cancer appeared one year and one month after the beginning of tar painting.

Only two mice developed recurrences at the site of tar painting. The recurrences are not counted in the number of mice with tar tumors, although, in view of the wide excision practiced with every tar cancer, they most probably represented new tumors.

As already stated, the tar cancers were removed by operation as soon as their malignancy was recognized. The animals of this group of "surviving cancer mice" died during the following year, mostly from intercurrent disease, or, more rarely, from metastatic growths in the lungs. If metastatic growths appeared in the axillary glands, they were removed by operation. It is interesting to note that the survival in the group of "cancer mice" was longer than in the "negative group." Thus, one year after beginning of tar painting there were, alive, thirty mice of the fifty-one mice which had developed tar cancer and only ten mice of the forty-nine mice which had shown neither warts nor tar cancer. Moreover, some of the operated surviving cancer mice were still alive in the third year of the experiment, while the last mouse of the negative group died twenty months after the beginning of tarring. Such a result lends no support to the view that in the induction of cancer by tar painting a "toxic" effect of the absorbed tar on the whole organism plays an important part.

(2) *The Papilloma Group*.—This group need not be discussed in detail, as all the animals of this group which survived the first year of the experiment had developed malignant tumors. There remain only the five mice mentioned above from which tumors had been removed as malignant new growths, which, on microscopic examination, proved not yet to have reached the stage of malignancy. They are therefore eliminated from the experiment. These five mice were alive at the end of the first year and remained negative during the second year, when they died.

(3) *The Negative Group*.—This group shows a gradual diminution as

the experiment proceeded, as the result either of the animals' developing tar cancer or of death from intercurrent diseases. Of this group ten mice were still alive at the end of the fifteenth month. They remained negative during the second year of the experiment, the last mouse dying twenty months after the beginning of tarring.

Results.—The actual data are given in Table I and represented graphically in Fig. 1. Using age periods of one month after beginning of tarring, the

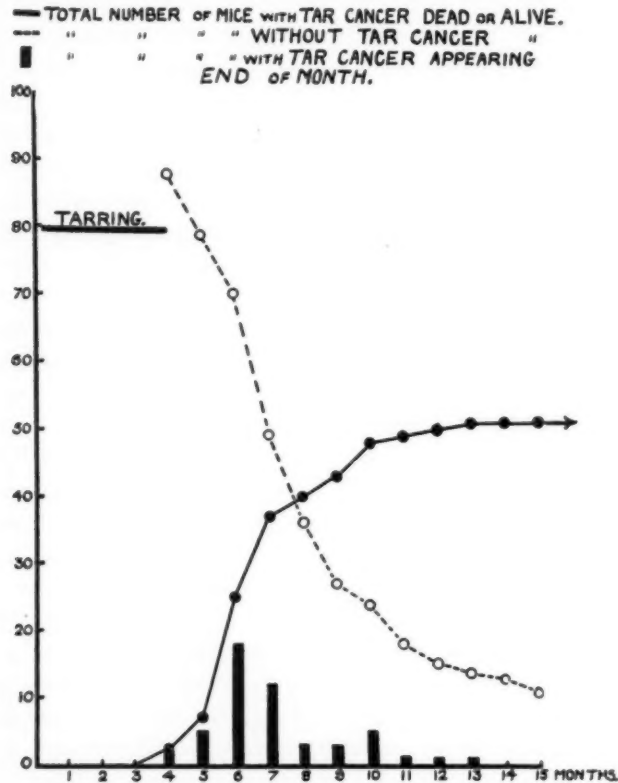


FIG. 1

figures given are: (1) The number of mice developing a tar cancer in each age period, and (2) the number of surviving non-cancerous mice for each age period (*i.e.*, papilloma group + negative group). From (1) and (2) it

TABLE I

Months from Beginning of Tarring	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Tar Cancers Appear- ing at End of Month	2	5	18	12	3	3	5	1	1	1	0	0	0	0	0	0	0
Non-cancerous Sur- vivors.....	88	79	70	49	36	27	24	18	15	14	13	10	6	3	3	1	0
Percentage of Tar Cancer in Non- cancerous Survivors	2.3	6.3	25.7	24.5	8.3	11.1	20.8	5.5	6.6	7.1	0	0	0	0	0	0	0

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is possible to calculate for each age period the percentage of non-cancerous mice which developed cancer. This is given in the lowest column of Table I and represented graphically in Fig. 2. It is necessary to elaborate these points in order to exclude the possibility that the marked decline in the appearance of tar cancers after the seventh month was due to a high death rate among the non-cancerous survivors. Fig. 2, which gives the percentage of tar cancers developing in each month in the group of non-cancerous survivors, shows that the percentage after having reached a maximum of 25 per cent. during the sixth and seventh months gradually declines to the zero line, indicating that the surviving mice remain free from cancer. In an experiment with continued tarring in which the surviving negative mice continue to be sub-

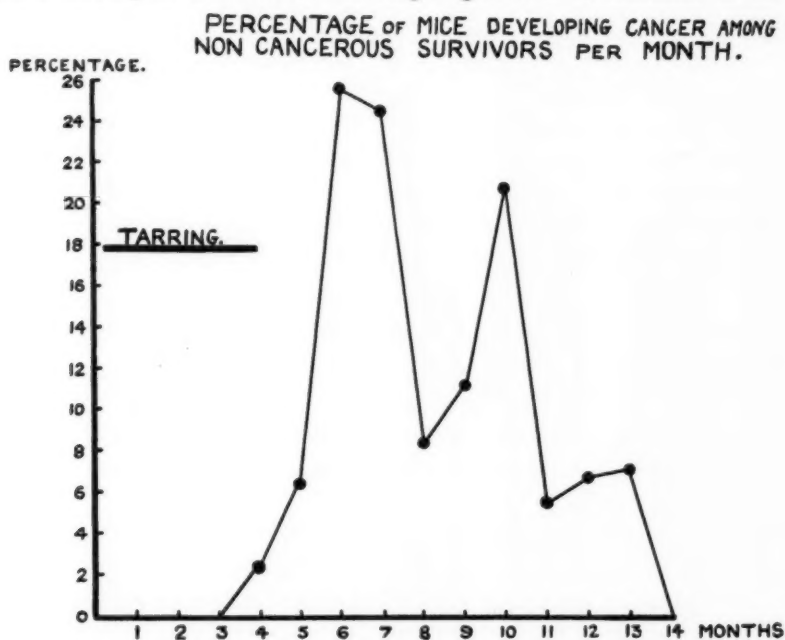


FIG. 2

jected to tarring until they also develop tumors, the curve representing the "total number of mice with tar cancer, dead or alive" shows a continual rise up to the end of the experiment, and so does the curve representing the percentage incidence of cancer in the negative survivors, while the curve representing the negative survivors shows a continued fall and eventually reaches the zero line, when all the surviving mice have developed a tar cancer.

The experiment with limited tarring shows conclusively that a degree of chronic irritation which is sufficiently severe to induce cancer in the majority of the tar-painted animals within the usual length of time (six or seven months) will show a greatly delayed carcinogenesis in a smaller group and will even leave a definite proportion free from cancer. Carcinogenesis by chronic irritation is therefore dependent upon a factor—or a group of factors

—which may be conveniently designated by the term “susceptibility,” or, if one uses a reciprocal term, “resistance.”

This phenomenon is of constant occurrence. Thus, in two further series of experiments on a smaller number of animals, mice were subjected to painting with the same actively carcinogenic tar preparation for four months. In each series fifty mice were treated in this way. On the thirteenth month after the beginning of tar painting the results were as follows:

	Carcinomata— Dead and Alive	Papillomata— Dead and Alive	Negative Survivors
First group.....	11	4	6
Second group.....	5	2	4

Reference may be made here also to an experiment carried out by Dr. R. J. Ludford (1929) in this laboratory and published recently. In this experiment, which was designed to study the effect of scarification on the induction of cancer by tar painting, two control series were made. In one, tarring was carried out for three months only; in the other, tarring was continued for each mouse until a papilloma appeared. The same tar preparation was used (Passey Tar). Twenty-five mice were tarred in each group. The results after the thirteenth month were as follows:

	Carcinomata— Dead and Alive	Papillomata— Dead and Alive	Negative Survivors
Continued tarring.....	8	5	0
Three months' tarring.....	8	1	4

In this experiment, continued tarring produced not only 100 per cent. of tumors, but the tumors appeared much sooner than in the group submitted to limited tarring.

It may be argued that in the mice subjected to limited tarring, the negative survivors would also develop cancer if they lived long enough. In our experiments, the negative surviving mice died without having developed cancer when they had reached an age of about one and three-quarters to two years; that is to say, they were middle-aged to old mice. They died from the natural risks to which the life of a mouse kept in laboratory conditions is subject. Even if it be admitted for the sake of argument that these mice would develop cancer if they could be kept alive long enough, the fact would remain that there are individual mice in which the onset of cancer is so greatly delayed that death occurs late in life from other causes, while in others cancer develops with comparative rapidity.

Anatomical Site of Resistance.—The factors which determine “resistance” or “susceptibility” may reside in the epithelial cells themselves, or they may be in the skin tissue as a whole, or they may reside in the organism as a whole. These possibilities, which do not mutually exclude each other, are capable of experimental investigation.

There is experimental evidence that the development of tar cancer can be influenced by conditions operating on the whole organism. Thus Maisin and

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his collaborators (1923, 1925) have shown that the induction of cancer in mice by tar painting can be accelerated by the injection of tar at a site remote from the tarred area. A similar acceleration has been observed by me (1926) in experiments on mice in which the spleen had been removed, minced and reintroduced intraperitoneally into the splenectomized mice. There are also peculiar features of the incidence of cancer in man which indicate the existence of systemic factors influencing the development of malignancy. Thus, in occupational cancer the disease develops only in a fraction of the individuals exposed to the chronic irritation induced by the occupation. What is more, some individuals may develop cancer although they have been engaged in the particular occupation for a few years only, while others, who have followed the occupation all their lives, remain free from the disease.

In the last two Annual Reports of the Imperial Cancer Research Fund, J. A. Murray (1928) and W. Cramer (1929) have discussed the bearing which international cancer statistics have on this point. The following figure, which is reprinted from the Twenty-seventh Annual Report of the Imperial Cancer Research Fund, shows that, while the recorded total incidence of cancer in the women of different countries is approximately the same, the recorded organ incidence varies greatly. It is even more remarkable that if a similar comparison is made for men and women of the same country, the same relationship is found. One must either dismiss these facts as a mere accidental coincidence, or one must attribute them to an underlying, systemic factor.

It is agreed that cancer develops as a result of chronic irritation. Cancer

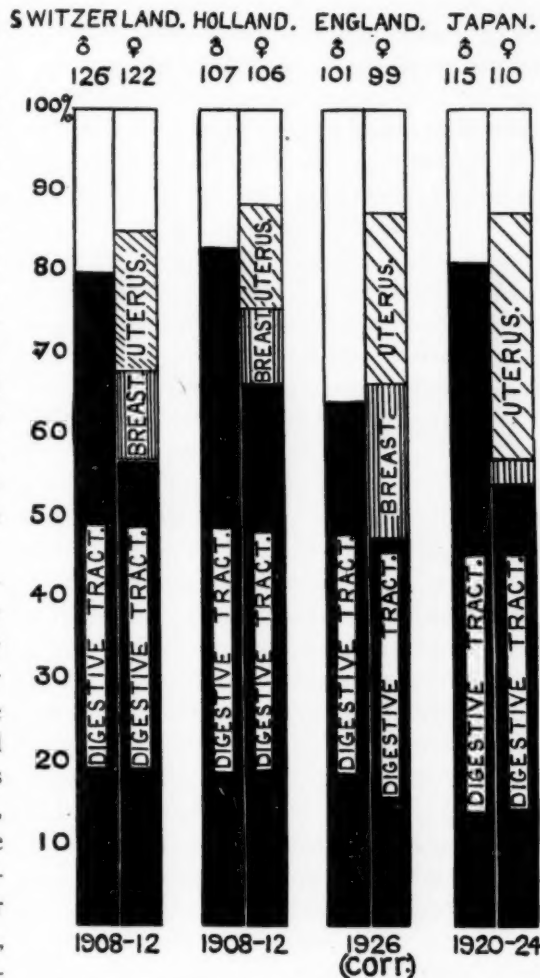


FIG. 3.—Comparison of the organ distribution of cancer in males and females in four countries. The line of figures at the top of the diagram gives the crude annual death rate per 100,000 living of each sex (except for England, for which the corrected rate has been taken). Reprinted from the Twenty-sixth Annual Report of the Imperial Cancer Research Fund.

will therefore arise most frequently in those organs which are most exposed to chronic irritation. These organs are, in men, the digestive tract; in women, the digestive tract, the mamma and the uterus. They account for about 75 per cent. of all cancer cases. It has been assumed hitherto that the incidence of cancer in man is determined entirely by the incidence of chronic irritation; that is to say, that when cancer develops in an organ of an individual, it is because that organ has locally been subjected to a certain amount of chronic irritation. That is, broadly speaking, true. But it does not follow—and in the light of our experiments it is not true—that the same degree of chronic irritation would produce cancer in other individuals. The experiments on mice given above have shown that the degree of chronic irritation necessary to induce cancer varies for different individuals, so that a degree of irritation sufficiently severe to induce cancer in some individuals will leave others free from the disease. The difference between an individual suffering from cancer and one free from cancer may be due to the fact that the former has been subjected to a more intense degree of chronic irritation than the latter. But it may also be the case that the degree of irritation was approximately the same but that there was a difference in the individuals subjected to it, the former reacting to it more readily by the development of malignancy than the latter. The incidence of cancer in man is therefore determined not only by the one extrinsic factor—the incidence of chronic irritation—but also by the intrinsic factor—susceptibility or resistance of the individuals whose organs are being subjected to chronic irritation. When, therefore, a comparison is made between the incidence of cancer in men and women of the same country, it must be borne in mind that in women there are three organs (mamma, uterus, digestive tract) which, being most exposed to chronic irritation, will pick out those individuals in which cancer develops most readily—the susceptible individuals—while in men there is only one—the digestive tract. This is sufficient to account for the fact that in men the incidence of cancer falls more frequently on the digestive tract. And since the total incidence of cancer is about the same for men and for women, although the organ incidence differs widely, the conclusion seems justified that the factor which determines the susceptibility to cancer of one organ is the same for the other organs.

Similarly, if a comparison is made between the incidence of cancer between the women of different countries, different habits of life will vary the degree of chronic irritation to which the organs in question will be subjected. Thus, if the habits of life in one country are such as to increase the processes of chronic irritation in the digestive tract as compared with another country, a larger number of susceptible women will develop cancer of the digestive tract and, therefore, fewer susceptible women will remain to develop cancer of the breast and uterus. This example accounts for the fact that Dutch and English women have an equal total incidence from cancer but a very different organ incidence.

The possibility that factors of susceptibility or resistance reside locally in

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the tissue subjected to chronic irritation was investigated by the following experiment.

A large area of skin was subjected to tar painting for a limited period, and any cancer which arose was removed by operation as soon as its malignancy was recognized, leaving behind the remainder of the tarred area. The results have already been published in detail (Cramer, 1929), so that they need be only briefly reviewed here. It was found that the appearance of the first malignant tumor was almost always limited to one centre. Even if the tarring was followed by the appearance of multiple papillomata, the malignant development occurred in only one of them, or in two closely neighboring ones. It was rare to find two carcinomata developing from two distant centres. After removal of the first cancer, a second cancer frequently developed after an interval varying from several weeks to several months. Under favorable circumstances—that is to say, if the mouse lived sufficiently long—the removal of the second tar cancer was sometimes followed by the development of a third tar cancer. In one case, a year and a half elapsed between the beginning of malignancy and the development of the second tar cancer. These experiments show, therefore, that the skin of one mouse may exhibit differences in susceptibility to tar cancer similar to those shown by different individual mice. It is clear, therefore, that some of the factors which determine resistance reside in the tissue itself.

The next question is whether variations in the susceptibility of a given tissue—in this case the skin—are determined by the epithelial cells or by the connective tissue, including in this latter term blood and nerve supply. The most obvious and most generally accepted conception of carcinogenesis is that the process is determined entirely by changes in the epithelial cells. If that were the case, differences in susceptibility would have to be referred to differences in the epithelial cells themselves. One would then have to make the *ad hoc* assumption that the skin epithelium is a mosaic of cells of a different inherent constitution. Carcinogenesis by tar painting of a small area would thus become a lottery, the result depending on whether the small tar-painted area happens to include a susceptible cell or not. The same would hold good for the development of cancer in man. The regularity with which experimental tar cancers develop with this technic is against such a view. Moreover, if this view were correct, negative results should be largely eliminated if a large area is subjected to tarring, since, under these conditions, the possibility of missing susceptible cells is excluded as much as possible. The technical difficulty here is that in the tarring of a large area more tar is absorbed, so that a toxic effect is produced on the animals and few mice survive the procedure. If one restricts tarring of a large area to tarring once a week, one finds again some mice surviving nine months without developing tumors, while the bulk of the animals has responded by the appearance of carcinomata or papillomata. Another experimental method of testing this question is the application of trauma to the epithelial cells. Deelman (1927) stated that persistent traumatization of the skin from outside, which stimu-

lated regeneration of the epithelium accelerated carcinogenesis by tar painting. Most observers have been unable to confirm this observation (Roussy, Leroux and Peyre, Ludford, Cramer). Ludford (1929), in the paper mentioned above, found that when scarification preceded tar painting, carcinogenesis was slightly retarded, and that when scarification followed tar painting carcinogenesis was inhibited almost completely.

But when a trauma is applied to the tarred skin from below—that is to say, when it is applied to the connective tissue—it has been possible in a number of cases to elicit carcinogenesis in a papilloma. Conversely, the inhibition of carcinogenesis by scarification, observed by Ludford, was attributed by him to the sclerosis following scarification.

The idea that the connective tissue plays an important part in the development of malignancy is not a new one. The experimental study of carcinogenesis has shown that, in the development of a carcinoma, changes take place not only in the epithelial cells, but also in the underlying connective tissue. Quite recently, Kreyberg has made an important contribution by demonstrating a well-defined series of vascular changes in the connective tissue of the tarred area, preceding the development of cancer. It is clear that a definite relationship must exist between the non-malignant epithelial cell and the connective tissue, and that this relationship is altered when the epithelial cell has become malignant. This is merely a restatement, in other words, of the fact that in regeneration and in benign hyperplasia the cells remain within the normal bounds set by the connective tissue, while in a malignant hyperplasia they invade it. Another experimental demonstration of this relationship is given when epithelial cells are transplanted from one animal to another. Both the malignant cell and the non-malignant cell elicit a reaction in the connective tissue. But with the non-malignant cell, this leads eventually to the destruction and removal of the implanted cells, while the malignant cell is able to dominate the reaction so as to compel the formation of a stroma which enables the implanted cells to live. Murray and Woglom (1921), in their investigations on experimental tar cancer, concluded that "progressive growth of autoplasts is proof of the cancerous nature of the growths which show it, even though, histologically, they may seem to be innocent."

A further example of the importance of the relationship between malignant cells and the stroma is afforded by the study of regressing tumors. Woglom (1922) has shown that regression may occur in a spontaneous, malignant new growth, the cells of which are still alive and even actively undergoing mitosis. He states that "a retrogressing carcinoma may be indistinguishable under the microscope from one that is increasing in size, or it may be totally keratinized or largely necrotic." Similarly, the external application of radium may bring about the regression of a malignant tumor by a process closely resembling that involved in the spontaneous regression (Cramer, 1905, 1928). The cells of a regressing, transplanted tumor can be inoculated successfully into other animals, although with a low percentage of "takes" (Bashford,

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Murray and Bowen, 1908). Similarly, the cells of a tumor which has received a dose of radiation sufficient to induce complete regression can be transplanted with a high degree of success into other animals, if the irradiated tumor is removed within a few days after radiation (Mottram, 1927). Further, one transplanted tumor can undergo regression while another tumor continues to grow in the same animal. Neither a change in the malignant cells alone nor a general reaction on the part of the organism can account for these phenomena. They can only be attributed to a local change in the relationship between the malignant cells and the stroma. It is possible to define exactly the part played by it in carcinogenesis. But there is a good deal of circumstantial evidence that in the transformation of hyperplastic epithelium into malignancy the connective tissue plays an important part and may be responsible for differences in susceptibility to cancer. Since the connective tissue pervades the whole organism and since its activity is subject to conditions imposed by the organism, it is possible to understand how susceptibility could be influenced both by local conditions and by the organism as a whole.

SUMMARY

Generally speaking, the experimental analysis of the process of carcinogenesis shows that this process is one which does not arise merely as the result of a direct action of a carcinogenic agent on epithelial cells, as is generally supposed, but that it is a much more complex one. In one sense, it emphasizes the local origin of the disease, for even if a large area of epithelial cells is subjected to chronic irritation, cancer arises only in a very small portion of this area. In another sense, it widens this conception by showing that the local development of malignancy is influenced by factors which do not reside in the epithelial cells but in the organism, and exert their activity presumably through the mesenchymal cell system. The terms "susceptibility to cancer" or "resistance to cancer" are intended to embrace the activity of these factors. The practical importance of these considerations lies in the possibility that the study of these factors may enable us to modify their activity in such a way as to delay, or even to prevent, the onset of cancer.

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HEREDITY AND CANCER

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WHEN physicians who have been for years and years in practice are asked whether hereditary factors are of any influence on the development of tumors, the answer is, in this country, usually in the affirmative. This is merely an impression, but an impression which has a value in the case of a disease which is so frequent as cancer. The frequency of cancer is higher in Holland than that of tuberculosis. The tuberculosis mortality decreases every year, while the mortality rate of cancer is constantly increasing. With Denmark and Switzerland, Holland has the doubtful privilege of being at the head of a series of countries with the highest cancer mortality rate.

When actual facts which support the assertion just made are asked for the answer is generally unsatisfactory. From time to time a family is met with which is said to be a cancer family, but of the behavior of cancer in general with respect to hereditary factors our knowledge is very slight. There are a great many questions connected with this subject for which no solution has been found. I might mention one of these. If hereditary factors really are of influence on the development of tumors, there are two possibilities. Either the influence is a direct one, or it works indirectly, by way of the hereditability of forms and functions of organs and systems. It is possible to imagine that a colon which is too long and a bad functioning of the stomach are hereditary conditions and that these abnormal conditions are of fundamental significance for the etiology of tumors. We are familiar with the same fact in tuberculosis. The form of the thorax may be a hereditary factor, the outbreak of the illness a direct consequence of this form.

In the field of human cancer study we have hitherto had to be content with few facts. The study on the experimental basis—such as Miss Maud Slye has carried out on mice—is much more hopeful. Nevertheless, research work on human material must be continued. In Holland, Doctor Wassink, the director of the Dutch Institute for Cancer Research in Amsterdam, published a study on this subject some years ago. He utilized the data which the patients who visited the institute were able to give him about the occurrence of cancer and other tumors in their family. The most important result of his study was that for some forms of cancer, hereditary factors could be demonstrated. For instance, in the case of cancer of the breast and cancer of the uterus, the occurrence of the same form of tumor in the family of the patients is much more frequent than would be expected from the annual statistical publications. For other forms of cancer this could not be established. For example, in the case of cancer of the buccal cavity, this form of tumor in the family of patients suffering from this growth was not more

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frequent than statistics would suggest. As to how cancer in general is related to family disposition, and particularly how cancer of the stomach—the most important form of cancer—behaves in this regard, the material of the Amsterdam Institute was insufficient. The question I put myself was the following: Is cancer in general in the family of cancer patients more frequent than in any other family in which there is at this moment no cancer patients? To my mind it is not advisable to inquire of the patients themselves as to their family data; it seems more likely to be successful to inquire of the physicians under whose treatment the patients are or have been. I therefore invited the collaboration of the physicians of the two northern provinces of the Netherlands, namely Friesland and Groningen. It may be supposed that during the illness of a cancer patient, or after his death, the physician has an opportunity of consulting the relatives about the appearance of cancer in the patient's family in former years. Physicians who have been for years and years in the same practice know something themselves about the family of their patients. I made another request to the physicians, namely

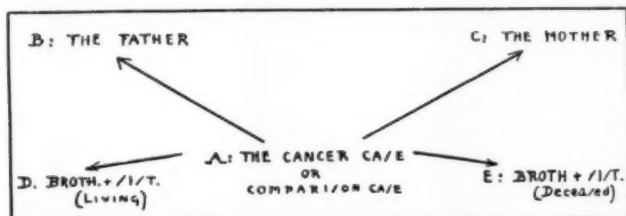


FIG. 1.

that they should send me along with the data regarding the cancer patient, the same data about any patient *not* suffering from cancer. They were asked to collect this data in precisely the same manner as the cancer data. Thus two series of family data were obtained. First, the data regarding the cancer patients; secondly the same about non-cancer patients of the same age. It is necessary to make the following remark concerning the coöperation of the physicians. In the northern parts of Holland, with their prosperous population, which has a firm belief in medical science and its representatives, the contact between physicians and patients is an intimate one. In the southern parts of this country this is not the same. Research work such as I mentioned above I consider to be possible only in the northern parts and especially in the country districts with a settled population. The urban population is useless for this purpose. At any rate, the data collected in this way are more reliable than information that patients can give themselves as to their relatives.

The forms which were sent to the physicians were arranged as follows: At A are placed the data regarding the cancer patient (or the comparison case).

At B and C we find the data regarding the parents of the cancer patient. At D, the data regarding the brothers and sisters who were still living, and at E what was known about their deceased brothers and sisters. In this

way data were collected regarding 350 cancer cases and about 250 comparison cases. It was found in practice to be difficult to furnish a comparison case for every case of cancer. The number of the former is, therefore, smaller than that of the latter.

First of all it is necessary to decide whether it is admissible to compare the two series of data received from the physicians. This was found to be actually the case. The ages of the two series of patients were the same. The same applies to the number of members of the families. This is an important point. In the two series of cases the number of brothers and sisters—both living and deceased—was equal. Moreover, the average ages in the two series were also the same. In such research work the unknown causes of death form a large group; more especially in the case of the parents, who died

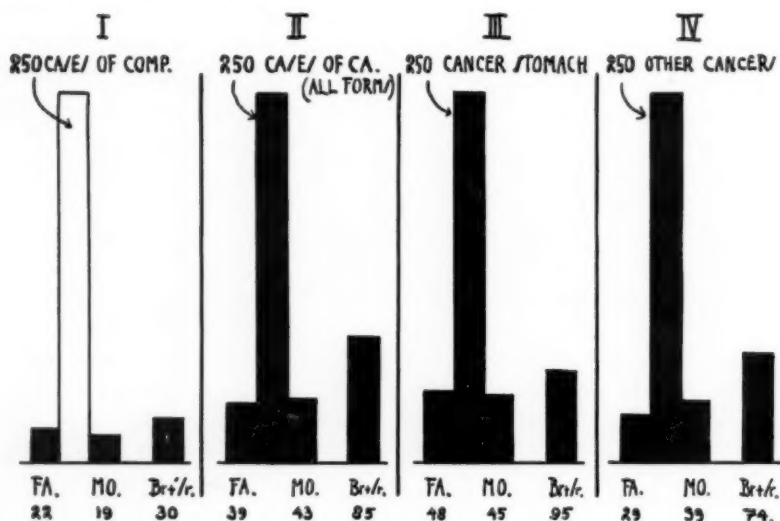


FIG. 2.

long ago, the unknown causes of death are a large category. We found in both cancer and comparison cases 21 per cent. of unknown causes of death. Thus in this direction the two groups of data were identical.

Here follow some of the figures as derived from the material. For the convenience of the reader I have drawn some diagrams in which the data are arranged in an easy manner. The cancer group is divided into two categories: cancer of the stomach and all the other cancers together. All the data are calculated for groups of 250 cases. Comparison is therefore immediately possible. In the first diagram are four sections. The first one (I) refers to the cases of comparison. The long blank strip represents 250 cases of comparison. Immediately to the left of this are placed the cancer cases which were found among the fathers of these 250 cases. Immediately to the right are placed the cancer cases among the mothers. Farther to the right will be found the cancer cases among brothers and sisters. The second figures (II) is the same grouping of 250 cases of cancer in general (black

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strip). The third one (III) is the same for cancer of the stomach and the fourth one (IV) refers to the cancer of all the other organs together.

In the group of cases of comparison (I) we found in 250 cases 22 cases of cancer among the fathers, 19 among the mothers and 30 among the brothers and sisters. In total in 250 cases of comparison we found in the family $22+19+30=71$ cancer cases. For the second group (II) (cancer in general) we found the following numbers: among the fathers of 250 cancer cases, cancer as a cause of death occurred in no less than 39 cases, among the mothers 43 cases, among the brothers and sisters in no less than 85 cases. In total among 250 cancer cases we found in the family $39+43+85=167$ cases of cancer. *In the cancer cases we found cancer more than twice as*

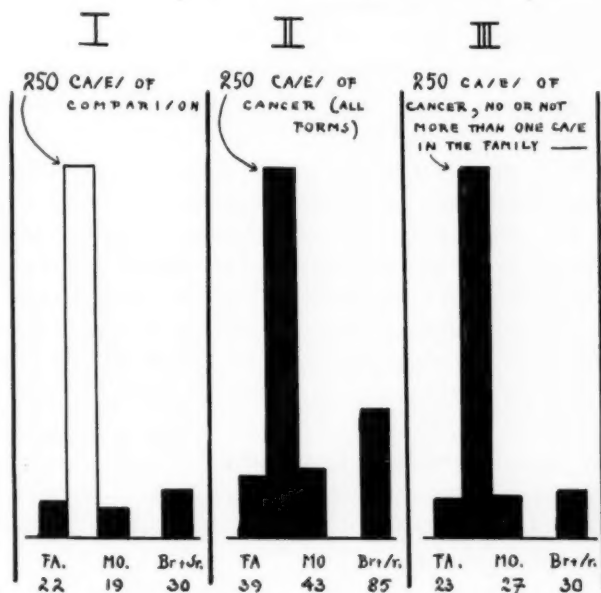


FIG. 3.

frequently among the parents as in the cases of comparison; in the group of brothers and sisters three times as frequently. For cancer of the stomach (III) and cancer of other organs (IV) we found the same differences as compared with the non-cancer series. For cancer of the stomach this difference was still more marked. The numbers are to be found in the diagrams III and IV.

The conclusion that can be drawn so far is this: Cancer is more frequent in the family of cancer patients than in any other category of families in which at the moment there are no cancer patients. The differences are more marked in the group of brothers and sisters than in that of the parents of the patients.

Many questions now arise. Among other things it would be interesting to know how cancer of different organs behaves in this respect. I did not wish to go farther than cancer of the stomach. The categories of other

organs were too small for analysis. We hope to do this in some years when the material has grown. The present material was collected over a period of three years. There is another question to which the material is large enough to furnish an answer: If cancer is more frequent in the family of cancer patients does the surplus of cancer cases appear without any regularity in the families of the patients, or is there an accumulation in certain families? Our material of 250 cancer cases has been divided into two categories. The first group contains all the cases of cancer, where two or more other cancer cases were found in the family. The second group contains all the other cases. In this latter group there was at most one other cancer case in the family in addition to the cancer case. The second diagram shows this. It is arranged in exactly the same manner as the first one. It consists of three parts. The first (I) and second (II) are the cases of comparison and the cancer cases. The third part (III) is the diagram of the cancer cases in which there were no other, or not more than one other cancer case in the family in addition to the cancer case. All the cancer cases with more than two other cancers in the family are crossed out. In this diagram it is evident that there is no difference between the last group and the cases of comparison. All the differences between cancer and non-cancer have disappeared. This shows that the group of cancer in general can be divided into two categories: One group where a distinct accumulation of cancer cases in the family was evident; and a second group of cancer cases where no more cancer appeared in the family than in the cases of non-cancer. Quantitatively the last group is much larger than the first (200:50). From this material we can draw the following conclusions:

1. In a series of families of cancer patients cancer is more frequent than in any other series of families.
2. The surplus of cancer in the family of cancer patients always accumulates in certain distinct families.
3. There is a large group of cancer patients in whose family cancer is absolutely not more frequent than agrees with the "normal" chance of dying of cancer.
4. Hereditary influences are only evident in a small category of cancer cases.
5. So far as can be judged from the material, there is no difference between the groups alluded to in 3 and 4 so far as the localization of the primary tumor is concerned.

IS CANCER A SYSTEMIC DISEASE?

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WHEN the average medical man of today hears the word "cancer," his mind will likely react thereto with the picture of a tumor, or, if he should happen to be one of those who, in recent years, has come to recognize the advisability of attacking cancer therapeutically in the precancerous state, he may see in his mind's eye a chronic dermatosis, a fistula, a benign tumor, or the like.

There seem to be as yet, however, but few clinicians who are willing to concede that precancerous lesions and malignant tumors are, in all probability, symptoms of preceding, more deep-seated morbid conditions, and that not unlikely a cancer-patient's whole system is abnormal long before any sign becomes noticeable which is commonly called suspicious. Their hesitation to fall in with such notions is readily understandable.

The conception of cancer as a systemic disease seemingly reverts to antiquated ideas which have been denounced as heresies by generations of medical men. These students sought in the cell alone the hidden secret of the cancer problem and, more or less, disregarded possible influences of the humors. However, in the light of the results obtained by the improved methods of investigation which we now command, this school appears to have been somewhat too radical in its condemnation of the systemic conception of cancer etiology and to have without proper justification declared obsolete the experience of the old-time keen-witted bedside physicians who diagnosed not from small specimens of excised tissue, but had always before them and examined the whole patient.

In this observance the writer believes we shall have to follow the example of the ancient general practitioners, if otherwise we want to succeed in curing a cancer in such a way that it will stay cured.

This statement is, though, by no means intended to imply that we should return to their mode of treating cancer and should continue where they left off. On the contrary, while recognizing certain points of view of these old-fashioned practitioners as well taken, we also realize that the intervening progress of the medical art has not brought us back in a circle to where they stood, but has lifted us in a spiral above them. The lofty height of present-day scientific achievement permits us to look down hopefully upon their struggles with obstacles which in those more remote times were found insuperable.

From this point of vantage a position appears now no longer tenable which regards a malignant tumor as a thing *per se*, as having a pathology of its own, as subject to none of the laws which govern the other parts of the body of its

host, and as capable of exhibiting in its cells powers which exceed those possessed by normal tissue cells. These views would seem to be erroneous.

In contrast thereto, it appears more likely that all cells, and consequently all cancer cells as well, are the creatures of the conditions which surround them; that they must adapt themselves to these conditions, or else perish; that cancer cells have no energy of their own; that the energy they seem to possess is imparted to them by the vis-a-tergo exerted through the growing cell multiplication and the demand for space of the daughter cells, and that therefore tumors of every description are not active, but passive growths. That is to say, they do not grow like a green leaf through inside forces, but rather like a heap of dry leaves through outside forces without any contribution to the growth on the part of the heap.

The views referred to as erroneous regard the tumor as the primary phenomenon and know systemic involvement only after the malignancy has become generalized. On the other hand, the here advocated view starts with systemic disturbances as the primary disease, on the basis of which malignancy sets in as a secondary development.

For those sharing the first-mentioned views, cancer is a cell problem; for those supporting the standpoint mentioned in the second place, cancer becomes primarily a problem of the physico-chemical condition of the humors of the body.

As a cell problem, the explanation of cancerous phenomena has admittedly run up against difficulties which leave these phenomena in darkness. As a physico-chemical proposition, the cancer problem finds thrown open for the overcoming of these difficulties formerly unavailable avenues of explanation which seem to lead to the light.

Under this latter conception the problem becomes a complex composed of "a constitutional disease cancer," conceived of as grounded in certain systemic disturbances; and secondarily thereto, of "a new growth cancer," as a symptom of the presence of the constitutional disease.

This conception brings forward a number of questions, which are: first, what is it that disturbs the normal constitutional balance of certain individuals and originates in their system conditions which seem to predispose them to cancer? Second, what is it that in some of these presumably cancer-susceptible individuals causes the onset of developments of potentially cancerous character? Third, what is it that, once these developments have been started, causes their continuance and turns potentially cancerous new growths into malignant tumors?

As stated and supported in previous publications,¹ the answer to the first question, as to the original systemic involvement, is believed to be an inherited or acquired imbalance of the sympathetic and para-sympathetic (vagus) nervous systems which induce a disturbance of the endocrine gland and serum electrolyte balance, and, in addition thereto, the reflex action of this latter imbalance to further increase the nervous imbalance, a vicious circle. This vicious circle might well be considered to be a "systemic chronic irritation."

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The existence of the vicious circle is diagnosable as vagotonia. Individuals exhibiting this symptom, which, by the way, is not specific for cancer, we believe to become gradually predisposed to cancer, as will be shown by taking up the second question.

The answer to the second question, as to what on the basis of the foregoing primary disturbances causes developments of potentially cancerous character, is based on the gradual increase of the degree of alkalosis of the tissue fluids through the intensification of the vicious circle. Weakness of the nervus sympathicus has also been shown in the previously mentioned publications to disturb by way of the parathyroid glands the calcium metabolism and to produce a deficiency of calcium ions in the serum. In this way the normal calcium-potassium ratio in the serum would seem to be thrown out of balance in favor of potassium, whereby the water economy of the patient's whole system becomes abnormal.

Inasmuch as potassium goes with cell swelling through imbibition, and calcium goes with cell shrinkage through desiccation, calcium deficiency, *i.e.*, relative potassium excess in the serum, is believed to result, by imbibition, in a hydropic condition of the cells of the entire body of an individual affected with a primary nervous imbalance.

As a consequence of the abnormally increased water content of the cells, there are found here, in addition to vagotonia, an impaired healing capacity of the tissue and sometimes a certain unnaturally florid appearance of the individual. As a result of the impaired healing capacity acute lesions leave behind in cancer-susceptible individuals various states of local chronic irritation. These states are of potentially cancerous character in such individuals because they are apt to induce cell proliferation if left untreated and permitted to increase in severity through the combined action of the prevailing disturbances. It may not be out of place to repeat our belief that they can so increase only on basis of the before-mentioned systemic chronic irritation and that without this latter disturbance a local chronic irritation may exist ever so long and not become cancerous.

In this assumption the answer is found to the third question, as to what causes the progress from potential to actual malignancy. As stated, it is based on the complex effect of the combined action of the systemic and local chronic irritation.

The effect of the local chronic irritation is cell death in the irritated tissue. In the streaming tissue fluids the dead cells undergo necrobiosis. Their detritus is washed away and absorbed. The detritus consists of cell lipoids and of the decomposition products of the cell protein, *viz.*, amino-acids and their derivatives. These protein products we have called "necrones," an abbreviation of necrohormones.

Necrones have been shown, also in the before-mentioned publications, to enforce the division of cells exposed to their influence. The divisions follow one another the more rapidly the stronger the necrone influence. It is assumed that the necrones go into solution with the cell lipoids and that the influence

of varying degrees of the concentration of this solution underlies all cell performances. A degree of concentration within the limit of the physiological tolerance of the cells for necrones is believed to cause cell function and the hypertrophy of resting cells, reversible by cell atrophy. A degree of concentration exceeding this limit is believed to enforce the onset of cell proliferation, reversible only by cell death. In the point of change from cell rest to cell motility we place the beginning of the precancerous state.

Inasmuch as this change requires a degree of concentration of the necrone solution which exceeds that physiologically attainable, the question arises as to how in the streaming tissue fluids it can materialize. Of course, it cannot. In order to materialize it needs stagnation. Where do we find stagnation?

Here recourse had to be taken to a working hypothesis. It is based on the well-known fact that cells are of varying resistance to chronic irritation. It has, therefore, been assumed in the previously mentioned publications that of the locally irritated cells some die, while others undergo merely an impairment of their permeability. A group of microscopic size of thus damaged cells may be called a focus within which, relative to the velocity of the streaming tissue fluids outside the group, more or less stagnation prevails, the degree of stagnation and therewith the degree of concentration of the necrone solution depending on the degree of impermeability of the cells forming the wall of the focus, *i.e.*, on the severity of the local chronic irritation.

We now have that which will force cells to divide: the concentrated necrone solution. The question remains to be answered, why do the cells continue to divide? The focus furnishes the explanation. Inasmuch as it furnishes the stagnation within which the necrone solution can form and become concentrated, it would seem also to protect the concentrated solution against dilution. The daughter cells of the cells that had their division enforced by the concentrated solution, on coming into existence, therefore find themselves exposed to the same influence that had enforced the division of their mother cells, so that they on their part are now forced to divide, as are also other generations of daughter cells after them as long as the local chronic irritation keeps up its slow increase in severity. When it stops doing this, the proliferative process will be arrested; when it decreases, there probably will be recession of the forming tumor; on its renewed exacerbation, the process will resume its progression.

If we now do as did the bedside practitioners of old and examine the whole patient, what do we find? We recall that we are dealing with a complex of active disturbances, the combination of the local chronic irritation and the systemic chronic irritation, the primary vicious circle. When we now make exact measurements of the serum reaction, they reveal that both disturbances have been gradually getting worse. The originally discovered predisposing low-grade alkalosis of the serum was of a so-called premetastatic degree, that is to say, cells newly formed at the focus and carried away in the lymph stream, lost therein their viability and underwent necrobiosis. Their

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detritus was absorbed and these cells disappeared completely. On reëxamination of the patient we now find a change to have taken place in the character of the tissue fluids. Their alkalosis has attained a degree in which disseminated malignant cells retain their viability. The serum has become metastatic and the vagrant viable cancer cells are apt to give rise to metastases.

Exact pH measurements have revealed the fact, as shown by the literature, that malignancy is always associated with a high degree of alkalosis, and it has also been shown that the alkalosis precedes the malignancy. There can be alkalosis without malignancy; but it would seem that there can be no malignancy without alkalosis. The more virulent the malignancy, the stronger must be the alkalosis which sustains it.

On examining our patient we find then that the combined effect of the systemic and the local chronic irritations has brought on a stage of the disease where, in consequence of the wide dissemination of viable cancer cells and the presence of metastases, the case would ordinarily be pronounced inoperable. But is there really nothing that can be done for such a case?

From the physico-chemical standpoint the answer appears obvious. If alkalosis is the *sine qua non* of tumor growth and tumor malignancy, why should not acidosis enforce the regression of the same? And so it seems to do, indeed. Close analysis of so-called miraculous cures, which hitherto had been left unexplained, has yielded this writer² the impression that acidosis produced in various ways, was the underlying cause of cure in all of them.

However, there are differences in degree clearly discernible. If the acidosis was merely relative, that is to say, if the alkalosis in which the malignant tumor flourished was reduced only to a lower level of alkalosis, there seemed to be temporary betterment and no cure. If clinical acidosis was produced, that is to say, acidosis below the normal blood reaction of the patient *i.e.*, below pH 7.39 to pH 7.33, in one instance pH 7.28 having been attained, there seemed to be a definite cure and the patient stayed cured for a number of years. Tumor and metastases had disappeared and the system had been cleansed of disseminated cancer cells, so that there was no more danger of recurrence of the former condition.

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THE INTERRELATION BETWEEN HEREDITARY PREDISPOSITION AND EXTERNAL FACTORS IN THE CAUSATION OF CANCER

I. NEOPLASMS IN MICE AT THE SITE OF GROSS TRAUMAS Studies in the Incidence and Inheritability of Spontaneous Tumors in Mice. 30th Report

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Two urgent lines of research in cancer confront us. First, studies in the etiology of cancers to the end that eventually, if it be possible, we may find methods of eliminating these diseases completely. This includes studies in hereditary predisposition which provide the susceptible individuals. Second, studies in the external provocative causes of cancers, in order that we may learn to prevent the development of cancers in persons susceptible by heredity. For these external irritations, which are not cancer-producing under ordinary conditions, when they are applied to a cancer-susceptible subject, seem to be an important factor in the occurrence of cancer. This fact gives us one of our greatest hopes for preventing cancer, until such time as we find a method of eliminating the disease, or in case we never find such a method.

The goal of the studies in cancer carried on in this laboratory has always been the collection of data concerning spontaneous cancers, which might aid in the prevention of cancers, rather than to seek for cures. It is for this reason that during the past twenty years I have put out some twenty-nine reports concerned chiefly with the etiology of cancer, the relation of hereditary predisposition to the occurrence of cancers, and the way these hereditary predispositions behave in cancer incidence, as this must be the fundamental background for future studies and for preventive methods.

As early as the second report of this series, however, in 1914, I recognized the importance of the external factor in cancer occurrence.¹ Again in the third report² I described at some length the relation of external provocative factors in the occurrence of cancers in mice with hereditary predisposition thereto. I stated as follows: "Tumors of the mouth and jaw are rare in mice. But there are just *two causes of chronic disorders in the oral region of mice, viz., the overgrowth and consequent pressure of an irregularly placed tooth, or a wound caused by fighting or by being hurt in the cage.*" I mentioned at that time female 7,618 (the subject of protocol 13 in this series) with her neoplastic growths at the site of a wound occasioned by an accidental blow from a cage door.

In later publications also, more or less casual reference has been made to the external factor in cancer causation. This matter was also discussed at length in the twenty-sixth report.³ But the hereditary predisposition, as

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the soil for the development of cancer, has always been particularly stressed. It is a somewhat difficult matter to collect a sufficient amount of evidence to be conclusive in showing the relation of external factors in spontaneous cancer causation. Hence I have delayed the report of this part of my studies until this time.

It is my intention now to put out a series of papers, of which this is the first, which will deal with data furnished in my laboratory, bearing upon the relation of external agents to the occasioning of spontaneous cancers. This first paper will deal only with the relation which external gross traumas seem to bear to the occasioning of cancers in susceptible subjects. It will include only those cases arising in my first 14,000 necropsies, in order that these may be handled in some detail, while still keeping the paper within the allotted length. Similar cases arising in the rest of the 92,000 necropsies performed to date must await later publications.

In the first 14,000 of these necropsies there occurred 1,301 indisputable neoplastic growths. Of these, fifty-one arose under observation at the sites of recorded gross traumas. Many more of these neoplasms may have been at the site of gross traumas, but the traumas were not observed at the time of their occurrence and by the time the growth was found the evidence of trauma was lost in the growth.

These fifty-one neoplasms were distributed as follows; twenty-four were in males and twenty-seven in females. This small predominance of females is unimportant, as the wounds of males are frequently received in fighting, and generally are so severe as to be fatal almost immediately, so that there is no opportunity for reparative processes.

These neoplasms occurred at practically every external site where wounds are possible. The locations were as follows:

- 5 in the testicle.
- 4 in the subcutaneous tissues of thigh and inguinal region.
- 5 in the mammary gland.
- 6 in the knee.
- 4 in the face.
- 7 in the subcutaneous tissues of the back.
- 1 in the outer aspect of the chest wall.
- 2 in the abdominal body wall at the base of the ribs.
- 2 in the mouth.
- 1 at the base of the throat.
- 3 in the foreleg and foot.
- 2 in the pelvis near a broken hip.
- 2 in the hip bone.
- 3 in the hind leg. (One of these mice showed liver and skull metastases, one showed pelvic extensions and the third had also thymus lymphosarcoma, retroperitoneal, pelvic and pancreatic lymphosarcomas.)
- 2 in the retroperitoneal tissues (with pancreatic extensions).

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- 1 in the prepuce.
 - 2 in the tail. (Both of these mice had leukemia also.)
 - 1 in the penis.
 - 1 in the subcutaneous tissues of the neck. (This mouse had also pseudoleukemia.)
 - 1 generalized throughout the subcutaneous tissues.
 - 1 at the base of the ear.
- In some cases wounds followed by neoplasms occurred in more than one site in the same mouse.

In addition to these mice wounded in external sites, there were also three cases of neoplasms in the liver which developed in male mice, each of which had been wounded and deeply bruised subcutaneously, immediately over the locations of the liver tumors. I am including their protocols as the juxtaposition of the subcutaneous wounds and the liver neoplasms suggests that the liver also may have been injured at the same time as the subcutaneous tissues. These cases may therefore be of interest.

TYPICAL PROTOCOLS

1.—♂ 585 was a member of strain 90, a highly tumorous strain. He was the son of female 31 with a sarcoma of the thyroid and a sarcoma of the thymus; and of male 167 that died of panophthalmitis. He was the grandson of female 3 (classic in these studies) that died of a mixed sarcoma-carcinoma of the mammary gland, a malignant adenoma of the liver and sarcoma metastases in the kidney. His grandfather, the brother of female 3, was male 30 that died of chronic interstitial nephritis and general amyloidosis without cancer.

This male 585 when about nine months of age, received minor injuries to the genitals in fighting. He was isolated for observation and while under observation developed a spindle-cell sarcoma in the left testicle upon the site of wounds. The immediate causes of his death, however, were myocarditis and oedema of the lungs.

The tendency to sarcoma in this line of the descent is notable, there being here three straight generations of sarcoma. The grandmother, female 3, with her mixed sarcoma-carcinoma of the mammary gland and sarcoma secondaries in the kidney, evidently in this line transmitted pure sarcoma. I consider this transmission of pure sarcoma (as well as pure carcinoma in some cases and mixed tumors in other cases) by female 3, as the best possible evidence for the very certain existence of these mixed tumors which have been under much dispute.

Male 585 is referred to on page 217 of the twelfth report⁴ of this series which deals with the testicular tumors in the first 19,000 necropsies of this work.

2.—♂ 596 was also a member of strain 90, having female 3 and male 30 for his grandparents also. His mother, 73, died of primary carcinoma of the lung, and his father, 752, died without cancer, of an unknown infection involving liver necrosis. He was the cousin of the foregoing male 585. He was isolated in "hospital" for observation after receiving multiple small bites on the genitals and upon the body. While under observation he developed a subcutaneous mass at the site of one of these wounds. The penis had been rather severely injured. The healing caused closure of the urethra,

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urinary retention and uræmia, which were the immediate causes of death. The subcutaneous nodule at the site of one of the wounds proved to be an adenoma. Adenomas and carcinomas occurred in the ancestry of this mouse.

3.—♀ 890 was a member of strain 264 which carried a number of tumorous individuals. The early generations of the strain have been charted and described on page 285 of the second report referred to.¹ It had at that time produced about 16 per cent. of neoplasms. The father and mother of male 890 both died before autopsies were begun. It is impossible to know whether they had tumors, but they had no external growths. Male 890 was badly bitten in fighting. He was isolated and under observation three weeks. He died of intrathoracic hæmorrhage, probably as a late result of his wounds. At autopsy a subcutaneous spindle-cell sarcoma was found on the left thigh at the site of a wound. Sarcomas, as well as adenomas and carcinomas lay behind this mouse.

4.—♀ 1376 was a member of strain 177 which produced many neoplasms. The strain has not yet been published. She was born on December 30, 1910, and died May 10, 1912. Her mother 260 died in labor without cancer. Her father was male 596 with the subcutaneous sarcoma described above. She was wounded in the inguinal region by her mate, male 1672, and was then isolated for observation. On the site of the inguinal wound there arose a small neoplasm which proved to be an adenoma of the mammary gland. Her death was caused by an abscess in the left kidney which also was sequel to her wounds. Adenomas and carcinomas lay behind this mouse.

5.—♂ 1470 was the parent of branch A of strain 53 which was charted on page 123 in the eighteenth report of this series.² His mother was female 3 already referred to in these protocols, and his father was male 40 that died of uncertain causes, the only abnormality found being a small cyst in the region of the urinary bladder.

This male 1470 was bitten about the genitals and on the belly. He was isolated for observation. He died about seven weeks later at the age of one year, five months, twelve days, showing at autopsy a hernia of the right seminal vesicle with urinary retention; right hydronephrosis; hypertrophy of the heart with pericarditis; œdema of the lungs and bilateral hydrothorax. He had also a malignant adenoma of the liver like his mother, female 3. This adenoma of the liver was in the vicinity of the belly wounds and suggests injury to the liver received at that time.

Male 1470 was mated with his sister, female 13, that had a mixed mammary gland sarcoma-carcinoma which closely resembled that of her mother, female 3. She had also pure sarcoma metastases in the lungs and mesentery. From this mating of two neoplastic mice (female 13 by male 1470) branch A of strain 53, a 100 per cent. cancer strain was derived. One hundred per cent. of the mice of this family that lived into cancer age (six months or over) had neoplasms.

6.—♂ 1506 was a member of strain 34, a tumorous strain made by the crossing of two tumor strains, both of which were in their origins hybrid derivatives of classic strain 90, and both of which reach back in their ancestry to female 3.

The mother of male 1506 was female 721 of the first generation of strain 21, that died of carcinoma of the mammary gland with metastases in the lungs. She was the granddaughter of female 3. She is charted in the fifth and seventh reports of this series.^{3, 7}

His father was male 2549, a member of the first generation of strain 41 (also derived from strain 90), and grandson of female 3. He died of intestinal infection without cancer.

Male 1506 was bitten about the genitals and belly. He was isolated for observation after being bitten the second time so badly as to cause closure of the urethra followed by acute nephritis and uræmia. At autopsy he was found also to have a malignant adenoma of the liver. Mated with his sister 3673 with a carcinoma of the mammary gland, he produced the 100 per cent. cancer branch of strain 34. One hundred per cent. of those that lived to cancer age had cancer.

7.—♂ 1717 was the son of adenomatous female 1376 described in protocol 4, and male 1672 that showed at autopsy interstitial nephritis and some necrosis of the liver tissue but no neoplasm. He was therefore the grandson of tumorous male 596 (protocol 2) and hence derived from original female 3. Like the two foregoing cases, males 1470 and 1506, he was bitten about the genitals and the belly, and was isolated under observation. At autopsy about two months later, he disclosed an adenoma of the liver adjacent to the subcutaneous wound.

These three cases, 1470, 1506, 1717, have been included here because all three were derived from the same original ancestry, namely, female 3, with a malignant adenoma of the liver; all three were bitten about the genitals and upon the belly; all three survived to make reparative processes about the external wounds; and all three disclosed at autopsy an adenoma of the liver immediately adjacent to the belly wounds.

8.—♂ 3117 was a member of branch IV of strain 146 frequently charted in this series of studies. See chart opposite page 164 of the third report² for this branch of the strain, and page 178 of the third report for the ancestry of strain 450, of which 3117 was a member. He was the son of double cancerous parentage; his mother 1805 had carcinoma of the mammary gland metastasizing in the lungs; his father 3553 had leukemia. His grandmother 529 had a mixed sarcoma-carcinoma of the mammary gland metastasizing in the lungs. His niece 5229 is described in the ninth protocol of this paper.

Male 3117 was picked up on the field of battle bitten about the genitals and on the mammary gland tissue of the left side near the axilla. He was kept under observation for about two months, during which time he developed a spindle-cell sarcoma involving both testicles, and a second spindle-cell sarcoma of the left axillary mammary gland. Six of his brothers also engaged in the fight, but 3117 was the champion, and the others died almost immediately of their wounds without reparative processes.⁸

9.—♀ 5229 was a member of the fifth generation of branch IV of highly cancerous strain 146. Strain 146 frequently has been charted and described in this series of studies. See pages 164-171 of the third report referred to² and⁹ pages 233-236 of the ninth report.

5229 was the daughter of cancerous female 3768 with four primary carcinomas of the mammary gland metastasizing in the lungs, and of hybrid carrier male 4933 that died of uncertain causes without cancer. She was the offspring of seven successive generations of cancer. Two of these generations had double cancerous parentage. Strain 146 was a hybrid derivative of 100 per cent. cancerous strain 139, which was also charted in both of the above reports. See page 164 of the third report and page 215 of the ninth report.

5229, at about eight months of age, was discovered on June 18, 1913, to have an early neoplasm in the left inguinal mammary gland. At this time her left hind knee had been hurt by being caught in the cage. She was placed under observation on this date and while under observation developed a hard growth on the knee at the site of the injury. Meanwhile her mammary gland cancer also progressed. She died August 3, 1913, at which time she was found to have a large alveolar carcinoma of the mammary gland and a fibrosarcoma of the knee.

10.—♂ 5695 was a member of the second generation of branch I, strain 150, frequently charted and described in these studies (notably in the twenty-first report¹⁰ and on pages 91 and 93 of the twenty-seventh report.⁸ He was the son of two hybrid carriers of cancer susceptibility, female 6488 and male 5426, both of which died of uncertain causes without cancer. He was the grandson of cancerous female 3383 with two mixed sarcoma-carcinomas of the mammary gland, and was a member of the sixth generation from male 274, parent of strain 145, with primary carcinoma of the lung.

Male 5695 was picked up on the field of battle July 8, 1913, badly bitten in sub-

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cutaneous tissues near the right shoulder. He was under observation from this date, and on September 15, 1913, showed a neoplastic growth at the site of the wound, which was then fairly covered with scar tissue. This growth extended dorsally to the mid-line, ventrally to the axilla and chest wall, and by the time the mouse came to autopsy measured forty by thirty-five by thirty millimetres. The growth proved to be a small spindle-cell sarcoma. Sarcomas, carcinomas and mixed tumors lay behind this mouse.

11.—♂ 6504 was a second generation member of strain 343 which is charted with its parentage in the third report on pages 174-176 and on page 291 of the ninth report of this series. He was the son of female 6357 with three carcinomas of the mammary gland metastasizing in the lungs, and of male 5850 that died of wounds without cancer. His immediate ancestry showed six consecutive generations of cancer, two of which had double cancerous parentage.

On December 19, 1913, he was found to have been bitten on both sides of the face and on the genitals. He was kept under observation until February 6, 1914, the date of his death. During this time he developed on both sides of the face at the sites of his injuries large fibrosarcomas which deeply infiltrated muscle, gland tissue and bone. He showed at autopsy also two papillary adenomas of the right upper and the left lower lobes of the lung. Sarcomas, carcinomas and adenomas lay behind this mouse.

12.—♀ 6629 was the daughter and the granddaughter of mice without cancer but they were hybrid carriers of the cancer tendency. Her maternal great-grandmother was female 529 with a mixed sarcoma-carcinoma of the mammary gland with metastases in the lungs. Female 6629 was bitten on both sides of the face by her mate, male 7470. While under observation she developed on the sites of these injuries bilateral spindle-cell sarcomas, and died in giving birth to her last litter of young (a litter of seven) on February 22, 1914, six weeks after receiving the wounds.

She was a member of branch IV, strain 164, which at the time of charting had shown cancer in about 24 per cent. of its members that lived six months or over. Charts showing this mouse and her ancestry have appeared in several reports of this series. For example page 500 of the fifth report.⁶

13.—♀ 7468 was the sister of female 6629 of the twelfth protocol. She was bitten on the back by her mate. At the site of this injury she developed a spindle-cell sarcoma which infiltrated through to the peritoneum. At autopsy her entire body was nearly bald, the wound on the back was covered with thick scar tissue and the sarcoma which distorted the whole body. The peritoneum proved to be extensively involved.

It is interesting to note in comparison with these two sisters, members of a highly tumorous strain, the reaction of many female members of non-cancerous strains, that have been wounded in the same way as females 6629 and 7468, without in any case the occurrence of a neoplasm.

14.—♀ 7618 was a member of 100-per cent. cancerous branch B of highly tumorous strain 84, frequently charted and described in this series of studies (especially on pages 115-122 of the eighteenth report).⁶ She was the sister of female 8702 with carcinoma of the mammary gland and primary carcinoma of the lung, and of male 11777 that died of carcinoma of the lung with metastases in the chest wall and kidney. For lack of space she was not included in the chart on page 116, but her background of cancer susceptibility is there shown.

On May 28, 1914, the left angle of the mouth of 7618 was deeply slit by an accidental blow from a cage door, that cut the face halfway to the eye and down on the chin. This mouse was, on this date, placed under observation, and as reparative processes went on proliferation in this region was very soon apparent. The mouse died on June 22, 1914, at which time at the site of the deep cut there was a tumor measuring twelve by ten by five millimetres which proved to be a squamous-cell carcinoma, beneath which there was a spindle-cell sarcoma. The blow had cut not only the epithelium

but also the deeper-lying connective tissues. There was, apparently an attempt at regeneration in both tissues, which resulted in a squamous-cell carcinoma on top of a spindle-cell sarcoma.

15.—♂ 7983 was a member of 100 per cent. cancerous branch A of strain 73. His ancestry is charted on page 155 of the sixteenth report of this series.¹¹ He was badly bitten in two places on the left side, the two bites involving the abdominal wall at the base of the ribs and dorsal thereto. At the site of each of these two wounds there developed a spindle-cell sarcoma, about eight millimetres in diameter each, that metastasized in the diaphragm on the pleural side, in all lobes of the right lung and in the inferior mediastinum. This mouse is described in some detail in the eighth report of this series.¹²

16.—♀ 8077 was a member of the third generation of strain 343, charted in reports 3 and 9 of this series. She was the daughter of double cancerous parentage. Her mother, female 7039, died of a carcinoma of the mammary gland metastasizing in the lung, and her father was male 6504 (described in the eleventh protocol), that died of bilateral fibrosarcomas of the face at the sites of wounds. Behind female 8077, therefore, in her immediate ancestry, there lay seven consecutive generations showing cancer.

She herself was accidentally struck on the mouth by a cage door in the hands of a careless diener. At the site of this wound, while under observation, she developed scar tissue, beneath and surrounding which was a spindle-cell sarcoma. At autopsy she showed leukemia which was verified by microscopic examination and blood count, and she had also lymphoid hyperplasia, and cystic degeneration of the mammary gland.

17.—♀ 8212 was a member of strain 367, an offshoot of strain 304 charted opposite page 172 in report 3² of this series and on page 164 of the sixteenth report of this series.¹ She was the offspring of three generations of double cancerous parentage and a member of a 100-per cent. cancerous family. Her great-grandmother 4514 died of a carcinoma of the lung (first diagnosed as adenoma and later as carcinoma). Her great-grandfather 5162 had tremendous subcutaneous lymphosarcoma extending from the neck to the inguinal region. Her grandmother 6685 had two spindle-cell sarcomas of the mammary gland. These tumors were first erroneously diagnosed as carcinomas but later, upon further study, they proved to be spindle-cell sarcomas. Her grandfather 7280 had a carcinoma of the lung and an adenoma of the lung. Her mother 7862 had carcinoma of the mammary gland and her father 8345 had squamous-cell carcinoma on the basis of a prolapsed rectum. Her four sisters, 7944, 7796, 8011 and 8960, all had carcinoma of the mammary gland. Her brother and mate 9944 had carcinoma of the lung and adenoma of the lung. The background here of cancer is thus very extensive.

Female 8212 was found with a subcutaneous wound at the base of the chest. While under observation she developed at this site a squamous-cell carcinoma in the midst of scar tissue over the wound.

18.—♂ 8579 was a member of cancerous strain 228 not yet charted in these reports. His mother 8125 had two carcinomas of the mammary gland, his father 6706 died of wounds, showing only advanced senile atrophy and little other change.

Strain 228 was a hybrid strain derived by crossing cancerous strain 47 with cancerous strain 146. The parents of strain 228 were female 3348 with two primary carcinomas of the mammary gland, and male 2805 that died of a liver abscess without cancer.

Male 8579 was bitten in the left inguinal region. At this point while the mouse was under observation, there arose a squamous-cell carcinoma with marked infiltration of the muscle. Such wounds in males of non-cancerous strains have never been followed by neoplastic growths of any kind during these studies.

19.—♂ 8986 was a member of cancerous strain 462 derived on the paternal side from strain 367, which in turn was derived from strain 304. As both of these latter strains were highly cancerous, there was a long line of cancerous ancestry behind male

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8986. His grandmother 8740 had squamous-cell carcinoma at the base of the ear. His grandfather 7730 died with senile atrophy, with few other gross changes, and without tumors. His mother 8836 had a fibrosarcoma of the abdominal wall adherent to the liver, probably at the site of an injury. But as this point is not perfectly certain, she is not included in this list of mice whose neoplasms certainly arose at the site of gross trauma. His father 8338 died of uncertain causes without cancer.

Male 8986 was found to have an injury on each knee. While he was under observation there arose a two-millimetre hard mass on each knee. These masses proved to be osteoid sarcomas.

20.—♀ 9128 came of a highly tumorous strain 16. She received two wounds on the back and upon the neck from her mate. At the site of these wounds on the back there arose scar tissue with a spindle-cell sarcoma beneath the scar tissue. At the site of the neck wound there was an abscess invading a second spindle-cell sarcoma. She had leukemia also.

21.—Male 9161 was a member of tumorous strain 135. He was accidentally cut across the right foreleg nearly to the bone, with the edge of a cage door. Two weeks later, on December 21, 1914, sarcomatous tissue was observed at the site of the wound. The mouse died January 9, 1915, with a spindle-cell sarcoma which involved the entire foreleg and the entire foot except the extreme tips of the toes.

22.—♂ 9293 was a third generation member of highly cancerous strain 338 repeatedly reported in these studies. He will be found on the chart of this strain opposite page 516 in the seventh report.⁷ In that chart he was stated as dying of wounds. He had been badly bitten about the genitals and the left hind leg. Upon the site of the wound on the left hind knee there was a hard nodule ten by eight by six millimetres. This nodule was not caught by the technician in making the first sections, and it was not until after the publication of this report that the nodule was decalcified and found to be osteoid sarcoma. This mouse had an immediate ancestry behind him of eight consecutive generations of cancer. His mother 10442 died of general sepsis from tapeworm, without cancer, and his father 11319 of a carcinoma of the lung. The neoplastic sequence in parents and grandparents of each generation behind 9293 was as follows:

- 1st generation: female with sarcoma-carcinoma of the mammary gland, malignant adenoma of the liver, and sarcoma secondaries in the kidney.
- 2nd generation: female with carcinoma of the mammary gland; and female with carcinoma of the lung.
- 3rd generation: female with carcinoma of the mammary gland and metastases in the lung.
- 4th generation: female with malignant adenoma of the liver; and female with malignant adenoma of the liver and adenoma of the mammary gland.
- 5th generation: male with carcinoma of the lung.
- 6th generation: female with carcinoma of the mammary gland, carcinoma of the pelvis and metastases in the lungs; and male with an adenoma of the lung.
- 7th generation: female with two carcinomas of the mammary gland; and male with adenoma of the liver.
- 8th generation: male with carcinoma of the lung.
- 9th generation: male 9293 with osteosarcomas at the sites of knee wounds.

23.—♀ 9350 of the same strain 338, also had a nodule on the knee at the site of an injury. This nodule also proved to be osteosarcoma. She died of hæmorrhage in the liver from tapeworm. She was the aunt of the foregoing male 9293 and appears on the same chart. As both of these nodules had to be decalcified, the final report on them had not been given when the chart was first published.

24.—♂ 9392 was a member of a 100-per cent. cancerous branch of strain, 186, published on page 501 of the fifth report of this series.⁶ His mother 2849 had desmoid tumor of the back and sides, as had also his father 3053, his sister 10054, his brother

10079, his son 10924 and his niece 12275. This was a small family, every member of which beginning with 2849 had this particular type of neoplasm on the back and sides, and no other type of neoplasm whatever. Male 9392 was found with wounds on the back and sides and was placed under observation. In this family this type of neoplasm ran a certain course. First the back and sides became completely hairless, then the skin and subcutaneous tissues seemed to be thickening so that the mouse gradually became almost unable to move. At autopsy the tumors all were of the same desmoid type. This is particularly notable as there have been very few desmoid neoplasms in my stock outside of this small family. In the case of male 9392 the tumor quite evidently arose at the site of wounds. If any superficial wounds preceded the tumors in other members of the immediate family they were not found in time to be certain that they preceded the tumor growth.

25.—♀ 9446 was a member of strain 449. She came of two generations of cancerous individuals. Her grandmother 6062 died of pulmonary infection without cancer. Her grandfather 5079 had spindle-cell sarcoma of the mammary gland. Her mother 7594 had two carcinomas of the mammary gland and lungs riddled with metastases. Her father 7472 died of uncertain causes without tumor, few changes being evident at autopsy.

9446 was found, on December 28, 1914, to have a small mass in the left flank. She also had slight wounds (from bites) in the left axilla and the left anterior mammary gland. She was placed under observation and during the period between December 28, 1914, and February 17, 1915, the date of her death, developed a second carcinoma (in the axilla) and a third carcinoma (in the anterior mammary gland) at the sites of the bites.

26.—♀ 9513 was a member of tumorous strain 135. She was the daughter of male 9161 of the twenty-first protocol herein, that died of spindle sarcoma involving the entire foreleg and foot to the tips of the toes, and which arose at the site of a deep cut. Her mother 8021 died when only three months old of uncertain causes without cancer. Her grandmother 4339 died of two carcinomas of the mammary gland with secondaries in the lung and mediastinum. She had also a primary adenoma of the lung. Her great-grandfather 1630 had carcinoma of the lung with metastases in the lungs.

9513 was found on January 5, 1915, with a broken left hip, with no recognizable tumor at the site of the injury. She was isolated for observation. She died February 24, 1915. I quote from the autopsy findings: "Within the pelvis on the left side is a tumor mass twenty by eighteen by eighteen millimetres which seems to have arisen at the point of the fractured hip from pressure of the broken bone. The tumor extends over the kidney but lies dorsal from the left horn of the uterus and involves neither organ." This mass proved to be an osteoid sarcoma.

27.—♀ 9554 was a member of strain 145 charted in the twenty-first report of this series. She arose three generations later than the last generation shown in the chart, but her ancestral background is therein shown. She was a member of a highly tumorous branch of her strain. Her grandmother was 3383, with two mixed sarcoma-carcinomas of the mammary gland.

9554 was found with a broken femur at the left hip on January 25, 1915. A small subcutaneous abscess on the hip had been noted November 12, 1914. This abscess cleared up, but it may have caused infection in the hip occasioning the later fracture. The mouse died March 1, 1915, at which time there was an osteosarcoma twenty by sixteen by sixteen millimetres arising at the fractured hip. She had been dragging this hind leg since the fracture noted on January 25. The sarcoma spread into the pelvis and retroperitoneal tissues, involving the peritoneum and the body wall. The liver was riddled with secondary nodules. The spleen contained a small secondary nodule in its upper surface and all lobes of the lungs were riddled with metastases. 9554 is described in the eighth report of this series, page 17.¹²

CAUSATION OF CANCER

At the sites of wounds described in the foregoing protocols, there arose neoplastic growths as follows:

12 spindle-cell sarcomas	2 adenomas
4 carcinomas	1 desmoid tumor
5 osteo- and osteoid sarcomas	3 fibrosarcomas.

Forty-two per cent. of these cases thus were spindle-cell sarcomas, while each of the other neoplastic types occurred in small numbers. I have also included in this series of protocols, three cases of liver adenoma in male mice. These adenomas were immediately adjacent to deep abdominal wounds, and this fact seems to suggest that the liver was injured as well as the subcutaneous tissues when the wounds were received. There are notable cases where more than one member of the same family developed the same type of neoplasm at the sites of similar wounds, and there is, behind every case, the significant neoplastic ancestry, particularly classic female 3 with her mixed sarcoma-carcinoma of the mammary gland, malignant adenoma of the liver, and sarcoma secondaries in the kidney, who was the original progenitor of many highly cancerous strains.

There have been in my laboratory, stocks which have never to date produced a neoplasm of any kind, either in their original strains or in their hybrid derivatives. Such strains I have called "non-cancerous" strains. Within these non-cancerous strains identical gross traumas have occurred quite as frequently as in the cancerous strains, without in any case the arising of neoplasms.

I have given herein only the facts concerning a very few of the cases arising in the first 14,000 necropsies of my stocks, where hereditary predispositions and recorded external gross traumas were both present, and seem to have been interrelated in occasioning the occurrence of cancers. Only the limit set upon the length of this paper prevents the presentation of many more such cases. The conclusion seems unavoidable that in the cases herein described hereditary predispositions and external gross traumas were the interrelated causes of the occurrence of cancers.

It is my intention, as quickly as possible, to put on record all such occurrences in my stocks, as well as the occurrences of neoplasms following other apparently cancer-provocative external factors. I shall not, at this time, speculate on this apparent interrelation between hereditary predispositions and gross traumas in the causation of cancers, nor upon its application. Only the first group of data is herein presented.

CANCER AND SMOKING HABITS

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POSSIBLY no phase of the highly complex cancer problem offers better opportunity for practical results than the general admitted correlation of excessive smoking habits to cancer of the buccal cavity, pharynx, larynx and œsophagus. Medical literature makes record of some outstanding illustrations from Emperor Frederick II of Germany to General Grant, who are known to have died of cancer of the throat attributed to excessive habits of smoking. Yet the question in general has not by any means been so fully elucidated by means of ascertainable and conclusive data as the urgency of the subject would suggest. In fact, I know of no really comprehensive statement of the whole question presenting modern facts suggested by the profound changes in smoking habits, including the wide extension of the practice of cigarette smoking to a considerable proportion of women.

It would not, of course, be feasible for me on this occasion to survey even the major aspects of the problem. But a few preliminary observations are called for in explanation of the medical data to be discussed in some detail, representing as they do entirely new information secured as part of my San Francisco Cancer Survey, and of other sections and localities.

Smoking habits in their relation to disease occurrence cannot possibly be considered without regard to

1. The kind of tobacco smoked.
2. The daily average quantity smoked.
3. The daily habits of smoking.
4. The form or method of smoking.
5. Date of commencing to smoke.
6. The regularity or irregularity of the habit in individual cases.

I can touch only very briefly upon some of these points by way of explanation. The nicotine content of tobacco varies widely in the different varieties. According to a recent report of the Connecticut Experimental Station, the total nicotine content of ordinary unprocessed pipe tobacco varied in eleven samples from a maximum of 2.8 per cent. to a minimum of 1.25 per cent. The average content for all samples of standard brands was 2.04 per cent.

In ten samples of standard brands of cigars, the range in nicotine content was from 1.90 per cent. to 0.91 per cent., the average for all samples having been 1.51 per cent.

In forty-six samples of standard brands of cigarettes the range in nico-

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tine content was from 3.34 per cent. to 0.43 per cent., the average for all samples being 1.77 per cent.

Hence it is shown that in the order of average nicotine content, cigars have the lowest average percentage, or 1.55 per cent., followed by cigarettes with an average of 1.77 per cent. and by pipe tobacco with an average percentage of 2.04 per cent. But these figures are of academic rather than of practical importance in that the actual quantity of tobacco smoked varies considerably as to whether the smoking is by means of pipe, or large-sized cigars, or from one to three packages of cigarettes a day. To ascertain the exact facts for a large number of individual smokers would, therefore, be quite a formidable undertaking.

Furthermore, daily habits of smoking differ enormously. Some persons (this applies to both men and women) smoke practically all day long, starting even before breakfast and ending just before going to sleep. Others smoke only after meals, and still others at regular intervals. Then again, some persons learned to smoke very early in life, say at ten or twelve years of age, while others acquired the habit late in life, when the possibility of injury must have been measurably less, particularly to the soft portion of the buccal cavity and the highly sensitive portion of the pharynx and larynx.

Nor can the profound changes in smoking habits on the part of the present generation be ignored. Cigarette smoking has very largely replaced the smoking of cigars, while the latter to a considerable extent have taken the place of the pipe. The use of the old-time clay pipe, in this country at least, has almost disappeared. In this connection I quote the following statement from the Commerce Year Book for 1929.

Cigarette production in registered factories passed the hundred billion mark for the first time in 1928, amounting to 105,927,000,000 in number, besides which 9,233,000,000 cigarettes for export were manufactured in bonded warehouses, making the total output 115,160,000,000. The average annual increase in production from 1920 to 1928 was about 7,300,000,000. The consumption of cigarettes in the United States in 1928 amounted to 102,765,000,000, an increase of 5.6 per cent. over 1927; the number per capita was 856 compared with 820.

As regards cigar production it is stated:

Cigar production during the last five years has shown little change, standing at a level somewhat lower than during the immediately preceding years or than before the World War. The output in 1928 was 6,874,000,000. The consumption of cigars in the United States, although not as great as before the cigarette became so popular, is larger than in any other country.

As regards the general effects of smoking on health, there is a variety of widely conflicting medical opinion. I may quote from a report by Dr. W. M. Johnson, which is rather favorable to the smoker, as pointed out by Dr. W. E. Evans, of Chicago, in an article on the subject. Doctor Johnson's conclusions are as follows:

1. Tobacco smoking apparently has no permanent effect on the blood pressure.
2. If it affects blood pressure at all, it temporarily reduces it.

3. It is doubtful whether tobacco plays a major part in causing angina pectoris.
4. The effect of tobacco smoking is chiefly local, exerted principally on the pharynx.
5. There is no foundation for the popular belief that smoking decreases the weight of an individual.

Nothing, in these observations, is said as to the possible correlation of smoking habits to cancer, which at the same time is one of the most striking phenomena of the practice.

The first question of importance for the present purpose is the extent to which smoking is practised in a normal population. There are some interesting statistics on this point in an article by Dr. Emil Bogan, of Cincinnati, contributed to the *Journal of the American Medical Association* of October 12, 1929. He gives returns for 630 men in an industrial population, of whom 282 were non-smokers, or 44.8 per cent.; 269 were light smokers, or 42.7 per cent.; and seventy-nine were heavy smokers, 12.5 per cent.

I have returns obtained by special investigators from living cancer patients in San Francisco, Buffalo, Boston, and some six or seven other cities representing a normal cancer population. Of the 1,416 male patients closely questioned 282 or 20.8 per cent. were non-smokers, 33.6 per cent. were moderate smokers, and 45.6 per cent. were heavy smokers. For cancer of the buccal cavity the respective percentages were as follows; non-smokers, 16.2 per cent., moderate smokers, 36.5 per cent., heavy smokers, 47.3 per cent. The percentages are based on 1,413 patients for whom smoking habits were ascertainable. In other words, for the entire group, 79.2 per cent. were smokers; while for cancer of the buccal cavity the percentage was 83.8 per cent. For cancer of the stomach it was 79.2 per cent. and for cancer of the intestines 66.3 per cent.

As regards particular smoking habits, I am afraid the returns are not entirely trustworthy, for it is seldom that a patient has only one smoking habit. In other words, a patient may almost always use a pipe but occasionally cigars also, while other smokers report the use of cigars and cigarettes in combination. Since there were 1,061 smokers, the number smoking pipes only was 349, but in addition there were 435 who admitted smoking pipes and cigars, a total of 78, or 73.9 per cent. For cancer of the buccal cavity only, this percentage was 81.1 per cent. Among heavy smokers, out of 607 patients returned as such, 232 smoked pipes only, while 223 additional smoked pipes and cigars, a total of 455, equivalent to a rate of 75 per cent. For cancer of the buccal cavity this proportion was 87.3 per cent. It is thus shown that the proportion of smokers is relatively largest among those who die from cancer of the buccal cavity and the same is true of pipe and cigars smokers, but the excess is not so marked as might have been expected. This, of course, is due to the fact that cancer of the buccal cavity represents a variety of tumor liabilities which have no connection with smoking habits, although it is highly suggestive that cancer of the buccal cavity is almost invariably much less common in the civilized populations among women than among men, but such cancers do occur.

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I have subjected my statistics to a critical analysis by specific organs and parts. Selecting a few for the present purpose it is observed as follows: There were sixty patients with cancer of the cheek, of whom eighteen or 30 per cent. were reported as heavy smokers. There were thirty-eight patients with cancer of the jaw, of whom seventeen or 45 per cent. were heavy smokers. There were 120 patients with cancer of the lips of whom fifty-seven or 48 per cent. were heavy smokers. There were thirty-three patients with cancer of the mouth of whom nineteen or 58 per cent. were heavy smokers. There were nine patients with cancer of the palate, and fifty-three with cancer of the tongue of whom thirty or 57 per cent. were heavy smokers. Among twenty-six patients suffering from cancer of the tonsils, thirteen or 50 per cent. were heavy smokers. Among sixty-eight patients with cancer of the œsophagus, thirty-four or 50 per cent. were heavy smokers. There were only three patients with cancer of the pharynx and five with cancer of the throat. There were thirty-seven patients with cancer of the larynx, of whom sixteen or 43 per cent. were heavy smokers. Finally, there were twenty-seven patients with cancer of the lungs, of whom eighteen or sixty-seven were heavy smokers. These wide variations are highly suggestive of the need of a much larger collection of facts for definite conclusions. But they are unquestionably indicative of a greater liability to certain forms of cancer among those who have acquired heavy smoking habits than among those who indulge normally. But as I have said before, it is extremely difficult to make sure that the statements regarding the habit are nearly accurate or measurably reported.

The foregoing results are strictly comparable with corresponding figures for non-cancer patients in San Francisco. These were patients suffering mostly from chronic diseases of adult life, chiefly heart diseases, arteriosclerosis, arthritis, hypertension, diabetes, nephritis, etc. I secured this information for 537 male patients and of these 236 or 42.3 per cent. reported themselves as heavy smokers against 45.6 per cent. for cancer patients and 47.3 per cent. for patients suffering from cancer of the buccal cavity. The differences are therefore very slight, which may be construed as opposed to the theory that smoking habits increase materially the liability to malignant tumors, particularly of the buccal cavity, œsophagus, larynx and lungs, but I would be reluctant to draw such a conclusion. Smoking habits may possibly constitute but one of a number of factors which must enter into the development of malignant tumors, the absence of any one of which might preclude such a development. Unfortunately the subject has not been studied as thoroughly as its importance would justify. But the observed excess in cancer of the buccal cavity in men, as well as in cancer of the œsophagus and the lungs, is highly suggestive of the influence of smoking habits, however difficult it may be to establish this conclusion statistically.

In the United States, among the white male population, in 1927, 5.8 per cent. of the cancer deaths were from cancer of the buccal cavity. For negroes this proportion was 5.6 per cent. and for Indians 5.5 per cent. For

Chinese it was only 2.3 per cent., which is highly suggestive since the Chinese are rarely addicted to heavy smoking habits. Now when these averages are compared with other countries, there appear some very surprising differences. The highest known proportion which I have been able to ascertain is for the white male population of Cuba, 1918-1922, or 14.6 per cent. This is followed by the male population of Mexico for 1928 with 13.8 per cent. Next in the order of importance comes the colored male population of Cuba with 11.7 per cent. This is followed with 10.8 per cent. for Australia, 1927, 10.3 per cent. for England and Wales, and the same figure for Scotland for the year 1928, and 10.4 per cent. for the European population of South Africa, 1922-1926. All these are measurably in excess of our American proportions. For New Zealand the proportion was 4.4 per cent.; for Shantung, China, Hospital, 1923-1926, 5.1 per cent.; for Buenos Aires, 1925, 7.9 per cent.; and for Canada, 1922-1928, 7.8 per cent.

Figures more nearly approaching those of the United States are those of Spain 1926, 7.3 per cent.; Manila, P. I., 1924-1925, 6.6 per cent.; Paris, 1924, 5.4 per cent.; Hawaii, 1924-1928, 3.7 per cent.; Holland, 1927, 3.5 per cent.; and Japan, 1924-1928, 3.4 per cent. This is the lowest figure of which I have record except for the Chinese of the United States, for whom, however, the numbers are very small.

Throughout the international comparison females invariably have a lower proportion of cancer of the buccal cavity than males, except the females of Manila. Here the proportion for 1924-1925 was 10.2 per cent., ascribed to the betel nut chewing habit, which includes tobacco and which is a direct causative factor in the development of cancer of the mouth, as also observed in Ceylon and South India. I would like to have given some additional figures for Egypt but unfortunately the sex was not separated in the return furnished me by the Egyptian Government. But out of 991 cases of cancer, all forms, during 1927-1928, 136 or 13.6 per cent. were cancers of the buccal cavity. The proportion therefore is relatively high.

In the United States in 1927, cancer of the buccal cavity for both sexes combined formed 3.1 per cent. of the total mortality from cancer. This is based on 3,184 deaths, of which 487 were deaths from cancer of the lip, 829 cancer of the tongue, 372 cancer of the mouth, 1,054 cancer of the jaw, and 442 from others of this class. In other words, a considerable proportion of deaths from cancer of the buccal cavity was from cancer of the jaw and others in this class, numbering in the aggregate, 1,496 or nearly one-half the total. Mortality from cancer of the buccal cavity represents types of malignant tumors in all probability very slightly connected with smoking habits. Cancer of the pharynx caused 1,044 deaths, or a rate of 1 per cent. of the total mortality from all forms of cancer, and cancer of the larynx caused 779 deaths, or 0.8 per cent. Cancer of the lungs and pleura caused 2,012 deaths, or 1.9 per cent. In addition, cancer of the œsophagus caused 1,756 deaths or 1.7 per cent. If, therefore, we combine the different forms of cancer most generally assumed to bear a direct relation to smoking habits,

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it appears that out of a total mortality from cancer of 103,578, 7,229, or 7.0 per cent., were attributable to the seven organs or parts in all probability most affected by smoking habits, a very substantial proportion well deserving of further and more extended consideration.

Indirectly the problem may be approached in another way. Smoking habits, unquestionably, during the last ten to fifteen years have increased enormously in this country until the practice has become almost universal among men, while it has been extended to women to an extraordinary degree. This practice refers chiefly to cigarette smoking, however, which by common consent is considered less harmful than pipe and cigar smoking as an irritant to the buccal cavity and the upper respiratory tract and possibly the lungs. I therefore examined into the deaths reported for different forms of cancer since 1915 with the following results:

Cancer of the lip in the registration area has remained stationary, prevailing at the rate of 0.5 per 100,000 in 1915, and 0.5 in 1927, rising in only one year to a rate of 0.6. Since pipe smoking and heavy cigar smoking has diminished during this period this result is not unexpected. Cancer of the tongue prevailed at a rate of 0.8 per 100,000 in 1915, and at the same rate in 1927. Occasionally the rate has gone down to 0.7 and in a few years it has risen to 0.9, but on the whole the rate has been practically stationary during the period under review. Here again also is evidence that the decline in the heavier types of smoking has left the situation of fifteen years ago practically unchanged. Cancer of the mouth prevailed at a rate of 0.4 per 100,000 in 1915, and 0.4 in 1927. During some years the rate has gone down to 0.3, but on the whole it has been practically stationary during the entire period under review, confirming previous observations with regard to cancer of the lips and tongue. For cancer of the pharynx unfortunately no trustworthy data are available until 1922. In that year the rate was 1.2 per 100,000 while in 1927 it was 1.0. Again the situation regarding this type of cancer conforms to that previously shown for cancer of the lips, tongue and mouth.

But when we consider cancer of the œsophagus, it appears that the rate has increased from 1.0 per 100,000 in 1915 to 1.7 in 1922. During the last six years, however, the rate has gone down, falling to 1.4 in 1924, rising to 1.6 in 1925 and 1.8 in 1926, but declining again to 1.7 during 1927. While therefore the rate is materially higher during the last eight years compared with 1915, it remains almost unchanged during these eight years although smoking habits have increased enormously. But it must always be kept in mind that the increase in smoking habits affects the different forms of smoking of cigarettes instead of the earlier and more common method of smoking pipes and heavy cigars.

Cancer of the larynx prevailed at the rate of 0.5 per 100,000 during 1915, rising to 0.7 in 1922 and 0.8 in 1923. It has remained at that figure year after year until 1927. Comparing the first year with the last there has been an increase but not sufficiently pronounced to be considered alarming.

When we come to cancer of the lungs, however, the rate starts with 0.7 per 100,000 in 1915, rising to 1.1 by 1920 and to 1.6 by 1924, and reaching a maximum figure of 1.9 in 1926 and the same figure for 1927. This increase in cancer of the lungs is by many authorities attributed rather to improved diagnosis than to a greater liability of the lungs to malignant diseases. This point of view I would be reluctant to accept. I am strongly inclined to think that the increase is directly connected with the much wider spread of cigarette smoking habits, including the inhaling of smoke which must enter the lungs to a considerable extent in many cases. But this would not be the only factor accounting for the increase, for there may possibly be a connection with the gross air pollutions of large cities as the result of motor cars. It is certainly significant, however, that out of seven types of cancer more or less connected with smoking habits, cancer of the lungs should at the present time show a higher mortality figure, or to be precise, in the order of importance, the lowest figure is for cancer of the mouth, or 0.4, followed by cancer of the lips, or 0.5, cancer of the tongue, 0.8, and the same for cancer of the larynx, cancer of the pharynx, 1.7, and cancer of the lungs, 1.9.

I have extended this analysis to England and Wales, for which standardized figures are available since 1901. The statistics for England and Wales, however, are for males only and must therefore not be confused with the corresponding figures for the United States registration area which are for both sexes combined. Cancer of the lips in England and Wales increased from 1.3 per 100,000 in 1901-1910 to 1.6 in 1926, declining to 1.2 during 1927. Cancer of the tongue remained practically unchanged, prevailing at the rate of 4.3 at the beginning of the period, rising to 5.1 during the next ten years ending with 1920, but declining to 4.4 in 1926 and 4.3 in 1927. For cancer of the mouth figures are available only since 1911. These show an increase in the rate from 2.4 per 100,000 at the beginning of the period of 3.0 during 1926 and 3.0 for 1927. Cancer of the pharynx increased from 1.1 during 1911-1920 to 1.3 during 1927. Cancer of the oesophagus increased slightly from 5.1 during 1901-1910 to 5.5 during 1911-1920, 6.5 during 1926 and 6.1 during 1927. Cancer of the larynx increased from 2.4 per 100,000 during 1911-1920 to 3.4 during 1926 and 3.2 during 1927. Cancer of the lungs increased from 1.0 per 100,000 during 1901-1910 to 1.3 during 1911-1920, with a much more decided upward tendency to 2.3 in 1926 and 2.3 during 1927. In a general way, therefore, the English figures confirm those for this country, but unfortunately they are not strictly comparable since the English figures are standardized for age variations during the years under review, while at the same time they are for males only, the combined figures for both sexes not being available. But they justify the assumption that cancer of the lips, tongue, mouth, oesophagus and larynx are unquestionably very much more common in England and Wales than in this country.

To make this point clearer, I am able to give comparable rates for cancer of the buccal cavity, considered as a group, for the two countries. In

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1927 the death rate from cancer of the buccal cavity for both sexes combined was 3.5 for the United States registration area against 8.0 for England and Wales. In 1920 the corresponding rates were 3.5 for the United States and 7.5 for England and Wales. It therefore admits of no controversy that cancers of the buccal cavity, considered as a group, are enormously more common in England and Wales than in this country. It is doubtful whether smoking habits are any more common on the other side of the Atlantic than on this; but I think it is a fair observation that Englishmen are much more addicted to pipes and cigars than Americans, who are more addicted to the cigarette habit. As I have previously shown, the proportion of deaths from cancer of the buccal cavity in the total mortality from cancer, all forms, was 10.3 per cent. for England and Wales against 5.8 per cent. for the white population of this country. The statistics are therefore apparently conclusive, but nevertheless suggestive of a much more extended study of all the facts of the situation bearing particularly upon the six points raised at the outset of the present discussion, every one of which bears upon the variations in the incidence observed. The method followed in my questionnaire examination of cancer patients if enlarged upon with particular regard to cancer and smoking habits would therefore in my opinion yield excellent results if pursued on a larger scale with due regard to international conditions than has been possible in connection with the San Francisco Cancer Survey.

Research in the literature of the subject has failed to bring forward extended observations on the subject. But I have not access to all the standard works on cancer in the different languages which might have proven productive of useful information at present unknown to me.

As regards cancer of the lips, Sir John Bland Sutton observes that "It is remarkable that though men are so much more liable to cancer of the lower lip than women, yet the liability is equal for both sexes in regard to the upper lip. Out of the thirty-one cases of cancer in the upper lip in Loos' total of 565, sixteen occurred in men and fifteen in women. The increased liability of men to cancer of the lip as compared with women is attributed to the greater frequency of tobacco smoking among men. In connection with this matter it may be mentioned that cancer of the lip is sometimes spoken of as 'countryman's cancer,' on account of the frequency with which it occurs among agricultural laborers, who use short-stemmed dirty pipes. The clay pipes with short stems are very convenient, as they can be carried in the pocket. In London hospitals some patients with cancer of the lip are farm laborers, but many are men who come under the term 'laborers' and their custom in regard to the short pipe is the same as the farmhand's. The stem of a short clay pipe soon becomes hot when in use, and burns or scorches the lip. Chronic ulcers caused by burns are prone to be the starting-points of squamous-celled cancers."

There are many other interesting observations by Sir John Bland Sutton which should not be overlooked. I can quote only the following, that "Cancer is occasionally seen in the lips of patients who do not smoke tobacco,

and who are not tainted with syphilis." This is precisely the point I would like to emphasize in the correlation of smoking habits to cancer of the buccal cavity and other parts of the body and upper air passages, that not all this mortality can by means be charged to smoking habits, and possibly only a small fraction. I regret that I have no data whatever for cancer of the upper or lower lip for this country since the facts are not taken cognizance of in the mortality returns. I add to the foregoing a brief quotation from an interesting discussion on cancer of the lip by William H. Kennedy, Indianapolis, published in *Radiology*, April, 1925. Doctor Kennedy observes that "The etiological factors in the production of this condition are still causing considerable discussion in all quarters. Although the use of tobacco-pipe smoking especially has long been regarded as being chiefly responsible for the appearance of the lesion in this particular locality, a sufficient number of cases have occurred in persons who never use tobacco to disprove this theory. And whereas smokers' burn has been given a prominent place in the etiology of cancer of the lip—benign in the beginning but later developing into a malignancy—the writer's personal experience leads him to conclude that the importance of tobacco in the causation of this condition has been overemphasized. In examining the histories of the 150 cases on which this article is based, it has, therefore, been concluded that the predisposing causes are undoubtedly of a complex nature and that no single agent can be held exclusively responsible for this malignant state of the lip nor of the cancerous condition elsewhere in the human organism." Doctor Kennedy, however, fails to draw the marked distinction insisted upon by Sir John Bland Sutton as regards the particular liability of the lower lip and its relation to pipe-smoking habits.

I have a brief note from the *Annals of the Faculty of Medicine of Montevideo*, December, 1925, in which there is an extended discussion on cancer of the lip by Dr. Carlos Butler, summarized in the statement, "Butler analyzes 173 cases of cancer of the lip and eighteen of pre-cancer conditions. In the 159 cases involving the lower lip, seventy-seven were smokers and fifty-one maté users. The total 191 cases included 8.8 per cent. women; in 23.2 per cent. the lesion was a post-operative recurrence. Under radium treatment, 60.3 per cent. were clinically cured and only 10 per cent. showed no improvement, in the lower lip cases, while 81.8 per cent. were cured and 18.19 per cent. improved in the upper lip cases."

Cancer of the tongue, in all probability, is only in rare instances connected with smoking habits. The etiological factor is more likely to be defective dental conditions often complicated by syphilis and resulting leucoplakia. Many years ago Sir D'Arcy Powers called my attention to syphilis in connection with cancer of the tongue, holding the opinion that he rarely saw a case in which syphilis was not present. Charles Ryall is quoted by Hastings Gilford to the effect that he had collected figures showing the relation of syphilis to cancer of the tongue and found that in over 80 per cent. of the cases cancer took place in a syphilitic subject. The same writer

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quotes Poirier's views that "Everybody cannot have cancer of the tongue; two conditions are almost indispensable—you must be a smoker or syphilitic; and those who combine those two conditions, especially the latter, have a much greater risk than other people. Cancer of the tongue might be called the cancer of syphilitic smokers."

Gilford Hastings, in discussing the question, remarks that "Tobacco acting as a strong local irritant is one of the sources of tongue cancer. Thus the causes of the leucoplakia which precedes cancer of the tongue are, according to Barker, 'Frequent abuse of alcohol, of spices, hot foods, and undoubtedly tobacco smoke' Leucoplakia was at one time termed 'smokers' tongue. Those who chew tobacco are also liable to this form of cancer, and Ewing says that these cancers often develop at the point where the quid is held. In Gibraltar and among the Spaniards of the neighborhood cancer of the tongue and lip is very common, and is attributed by Turner, of the Colonial Hospital, to excessive cigarette smoking."

Cancers of the lip and tongue are, of course, subject to remedial treatment and the mortality figures must be considered affected by the results of such treatment which to an increasing extent are suggestive of a hopeful outcome. Radiology in this respect has made immense progress with encouraging prospects for the future.

In my "Mortality from Cancer Throughout the World," in discussing the cases treated at the New York State Institute for Malignant Diseases, I give a number of illustrative cases showing, for example, that for cancer of the lip there were twenty-two deaths at an average age of seventy-four years in which smoking was the probable cause of fourteen. Other causes alleged were a cut on the lip in one, ulcer of the lip in another, a wart in the third, and a tooth in a fourth. There was a personal history of alcohol in three cases, of syphilis in only one. I give an analysis of twenty-three deaths from cancer of the tongue at an average of sixty-eight years, in which the probable cause was smoking in twelve, irritation from a tooth in three, while there was a personal history of alcohol in six, and syphilis in only one. There were four female deaths from cancer of the tongue in which the probable cause was given as smoking in one. The Gibraltar case is mentioned in my "Mortality from Cancer Throughout the World," being derived from the Colonial Office correspondent in connection with the Imperial Cancer Research Scheme. In this it is said: "Probably three-fourths of all cases of cancer met with in the practice of the Colonial Hospital, have their seat in one or the other of these organs. The predisposing causes of cancer, in this part of the world, appear to me to be, in males, excessive tobacco smoking, leading to irritation of the lips and tongue; in females, premature child-bearing and lactation. The Spaniard's cigarette or cigar is never absent from his lips if he can help it, and he allows it to burn so close that the actual fire must frequently char the epithelium of his mouth."

I have shown previously that cancer of the buccal cavity in Spain caused 7.3 per cent. of the total deaths from cancer against 5.8 per cent. for the white

population of the United States and 14.6 per cent. for the white population of Cuba, where the population, as in Spain, is likewise addicted to excessive smoking habits. The same is true of Mexico City where the proportion is 13.7 per cent. or the second highest in the international compilation previously dealt with. It is highly significant that in Cuba among the white female population, cancer of the buccal cavity should be as high as 4.9 per cent. against 1 per cent. for the female white population of the United States and 6.1 per cent. for the colored female population, while it is 4.5 per cent. for the female population of Mexico City, and for Spain in marked contrast, the proportion is only 1.5 per cent. but still markedly higher than for the white population of this country.

Cancer of the œsophagus is such a serious affection that changes in the death rate during recent years are not very likely to reflect to any measurable degree improvements in treatment. The affection was the cause of 1,756 deaths during 1927 in the United States registration area, equivalent to a rate of 1.6 per 100,000, or 1.7 per cent. of the total mortality from all forms of cancer. Since 1915, as I have had occasion to point out, the rate has increased from 1.0 to 1.7. In England and Wales the actual mortality from cancer of the œsophagus has increased from 5.1 per 100,000 for males to 6.1 between 1901 and 1927. The disease is therefore decidedly more common in England and Wales than in this country even though precise figures for comparison for males only are not available. The œsophagus, according to Cunningham, "is the narrowest and at the same time one of the most muscular of the alimentary tubes." Being extremely narrow it is therefore subject to no end of irritation during the process of alimentation, giving rise no doubt to numerous causative conditions favorable to malignant growths. The relation of smoking habits to cancer of the œsophagus must therefore in all probability be one of many factors explaining the relatively high incidence of this affection in males, who suffer decidedly more than women. While the death rate for cancer of the œsophagus is 6.1 per 100,000 for males in England and Wales, it is only 1.5 for females, or about the same rate as prevails for both sexes combined in this country. For females in England and Wales the rate has increased from 1.5 in 1901-1910 to 1.8 during 1927. This might possibly be related to the immense increase in smoking habits in England among women during recent years.

Dr. William Hill some years ago, in a discussion before the Royal Society of Medicine, pointed out that the statistics of cancer of the œsophagus have been falsified by the inclusion of many cancers of the pharynx. This in all probability has been the case in this country previous to 1922 on account of which I have not used the statistics of cancer of the pharynx for the earlier years in my comparison. If this explanation is accepted, deaths from cancer of the œsophagus in this country have increased probably much more than the indicated growth in the rate from 1.0 in 1915 to 1.7 in 1927. That this increase is, in part at least, attributable to smoking habits cannot be denied although the positive evidence may be wanting. In the etiology of

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cancer of the œsophagus, much more stress is generally placed upon hot foods and hot drinks, or alcoholic drinks, than upon smoking. Fischer, in the *Clinical Weekly* in 1924, makes reference to the alleged frequency of cancer of the œsophagus in the Chinese and the view that it was due to the eating of hot rice, but this view he rejects. He observes, however, with regard to the etiology of cancer of the œsophagus that, "There are many facts in favor of the view that it is excited by chronic irritation." He adds that "Cancer is most liable to develop at the three points where the œsophagus is narrowest. The disease is much more common in men than in women. The influence of alcoholic excess has been much disputed. In Argentina the disease has been regarded as the result of drinking very hot 'maté'; in China the drinking of hot arrack has been regarded as an exciting cause." In this he does not mention smoking at all and leaves the situation as confused as before.

Somewhat earlier, in the *British Medical Journal* of December 8, 1923, Dr. William Hill, London, attributed cancer of the œsophagus primarily to excessive drinking of concentrated forms of alcohol or of excessively hot fluids. Here he observes in this connection that "In my investigations the number of those individuals who were found to be the victims of cancer of the œsophagus who gave a clear history of excessive drinking of either ardent spirits or very hot fluids or both has not been such as to impress me with the correctness of alleged association implying cause and effect." He also leaves the confused situation unchanged. It is significant that he should make no mention of smoking habits. An extended discussion of cancer of the œsophagus by Dr. J. Guisez of Paris, at the University of London, in 1924, fails to mention tobacco as an exciting cause, although mentioning chronic irritation of alcoholic origin. Mention may be made of a statement by Ropke, a German authority, according to which there are twenty-three cases of cancer of the œsophagus in men to three in women, and that he believes that this disparity is due to the influence of alcohol and tobacco. With this statement I concur.

In cancer of the larynx it is reasonably certain that smoking habits play an important part. In the British figures the mortality from cancer of the larynx is given as 3.17 per 100,000 for men and as 0.7 for women. Hence we have here the same decided disparity between the two sexes as observed in cancer of the œsophagus and buccal cavity. Many of those who have written on the subject have attributed to smoking habits direct causative results in cancer of the larynx but I am not aware of any exhaustive study from a statistical point of view. Most of the references available to me are of no particular value in supporting the conclusion one way or the other. I, however, can see no reason why the larynx should not be particularly susceptible to the irritating effects of tobacco smoking, granting that the latter is productive of cancerous affections.

In cancer of the lungs the effects of tobacco smoking are more difficult to prove but there is not the slightest question of doubt as to the fact that those who practise inhaling certainly drive the smoke into the innermost

recesses of the lungs. The observed increase in cancer of the lungs during recent years is highly suggestive of its correlation to the immense spread of cigarette-smoking habits. In the English statistics the mortality from cancer of the lungs for 1927 was at the rate of 26.8 for men and 9.7 for women. Here again the disparity in sex susceptibility is highly suggestive of smoking habits as a causative factor. But cancer of the lungs has been attributed to a variety of modern conditions which may account more or less for the observed increase which cannot be entirely, at least, attributed to better diagnosis. In England and Wales cancer of the lungs has increased in males from 0.2 during the ten years ending with 1910 to 26.8 during the year 1927. In females the rate has increased during the same period from 7.0 to 9.7. Yet smoking habits have proportionately increased faster among women during recent years than among men. But the fact must not be lost sight of that the injurious effects of tobacco smoking in their relation to cancer probably require quite a long period of time to become noticeable. Since I have dealt with the question of cancer of the lungs in a separate discussion published in the *American Journal of Tuberculosis*, I will not enlarge upon it on this occasion, except to say that personally I am strongly of the opinion that a relation between the increase in smoking habits and cancer of the lungs may safely be assumed to exist. I have never been inclined to accept the view that the increase in lung cancers during recent years is chiefly attributable to the after-effects of the influenza epidemic. As observed in the *Journal of the American Medical Association* of February 13, 1926, the clinical records in a large proportion of the investigated cases did not show any history of influenza.

How far smoking habits may affect other organs and parts in their specific liability to cancerous affections involves difficulties which do not admit of being dealt with on this occasion. I am full well aware that there are those who maintain that the increase in cancer of the stomach bears some relationship to smoking habits.

Lickint, among others, has advanced the following conclusion: "Nicotin decreases the action of pepsin and of rennet. Potassium sulphocyanate, found in excess in the saliva of smokers, has an inhibiting effect on protein digestion. In chronic smokers, the peristalsis is first increased, later decreased." He therefore believes: "Tobacco may play an etiologic rôle in neuroses of the stomach, in disturbances of its secretory function, in gastritis, and even in ulcer and cancer."

But so many factors enter into gastric cancers that it is extremely difficult to isolate the pronounced effects of any one particular factor in a satisfactory manner. I shall presently consider some more extended observations of Lickint in his most recent contribution to the *Journal of the German Society for Cancer Research* in which he covers the entire field, although in rather a superficial manner, but amplified by a large number of references extremely useful to the research student.

Before I consider these observations I would like to emphasize briefly

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certain additional aspects of the cancer problem generally overlooked. The natural duration of cancer has been subject to much discussion though rarely dealt with on the basis of adequate data. In the nature of the case the natural or known duration of the disease can at best represent but a scientific guess upon a more or less confused state of facts. The onset of cancer is too obscure in the human body to permit of being determined, except in rare cases of trauma, with absolute precision. I have therefore used the term "known duration of cancer" as given on the death certificate by the attending physician. Since cancer is not a painful disease at the onset, more or less conjecture enters into every individual determination of disease duration. In my San Francisco Cancer Survey I have tabulated the known duration of the disease for a large number of organs and parts and in most cases on the basis of a fairly large number of observed cases. Selecting fourteen different organs and parts for purposes of comparison, the known duration of the disease in all my tabulated deaths for different localities and sections of the country, including eight years of observations in San Francisco, has been as follows: The known duration, previous to death in males, was longest in cancer of the lip, or 25.1 months. This was followed by cancer of the prostate with 20.3 months and cancer of the bladder with 17.5 months. It was 16 months in cancer of the rectum, 14.9 in cancer of the tongue, 14.9 in cancer of the liver, 13.9 in cancer of the intestines, 13.6 in cancer of the jaw, and the same or 13.6 months in cancer of the stomach, 12.8 in cancer of the larynx, 10.1 in cancer of the lungs, 9.3 in cancer of the œsophagus and 9.0 in cancer of the pancreas.

These are the statistics for male deaths only for American cities. For certain Canadian Provinces and cities the results on the whole fairly conform to those for the United States, particularly cancer of the lip, which shows an average known duration of 26.7 months, followed by cancer of the bladder with 18.5 months. But the Canadian returns are numerically less trustworthy. Hence in estimating the effects of the growth of tobacco smoking, some allowance must be made for the probably much longer natural duration in cancer of the lips, as, for example, compared with cancer of the tongue, œsophagus and the lungs. But in any event, the known duration of the disease before death is at best but a matter of conjecture however well statistically established. The known duration of the disease previous to death must not be confused with the known duration previous to the time the patient received his first medical attention. It would seem, however, that the duration in no case is sufficiently long to offset the prodigious rise in tobacco consumption in this country during recent years.

In an address on "The Causal and Formal Genesis of Cancer," read by Doctor Ewing at the London Cancer Conference in 1928, occurs the remark: "One will hardly err in accepting the conclusion of the older clinicians that cancer of the mouth would disappear if tobacco, bad teeth, and syphilis could be eliminated." In his earlier address at the Mohonk Conference in 1926 Doctor Ewing said: "Among preventable cancers the most obvious is the

intra-oral group. It has long been known that cancers of the lip, mouth, tongue and tonsil are due to bad teeth, tobacco and syphilis and the importance is, I think, in the order named. Experience in a large clinic for these diseases reveals, on the average, an astonishing degree of irritation due to these factors." And in continuation, "Cancer of the lip is nearly always caused by the irritation of tobacco but a prominent predisposing factor is seborrhœic dermatitis and inflammation of the vermilion border. . . . The use and especially the abuse of tobacco must be charged with a large share in the production of intra-oral cancer as well as of cancer of the larynx and probably of the œsophagus." Finally he remarks: "One may hardly aim to eliminate the tobacco habit, but cancer propaganda should emphasize the danger signs that go with it."

While there is apparently a reasonable consensus of qualified opinion as to the injurious effects of heavy smoking habits, no light is thrown upon the real nature of the problem as modified by various considerations to which I have drawn attention at the outset, for the changes in smoking habits have introduced forces, the effect of which it is difficult, if not impossible, to measure. Dr. W. Blair Bell, of Liverpool, for example, has expressed the opinion: "Cigarettes, without holders, and cigars were not so dangerous, because they were held in all parts of the mouth. But in the case of pipes and cigarette-holders it was found that the stem could be held in the mouth most comfortably in one particular position. The result was that over a period of years a hot stream of smoke was directed on to a particular part of the mouth or tongue, producing an irritant sufficient to account for the precancerous condition." The habit of using cigarette-holders as yet is rather rare. Most men smoke cigarettes without holders, but in many cases they smoke the cigarette too near to the mouth so that a burning sensation can be distinctly felt. In the case of cigarette-holders there is much variety of varying degrees of heat conductivity. The difficulty with many cigarette-holders is that they permit the cigarette to be smoked to the very limit of combustion, thus probably increasing the degree of heat which reaches the membranes of the buccal cavity, much more so than in ordinary cigarette-smoking habits. Unless regard is paid to this factor a correct answer to the question as to how far smoking habits are causative factors in buccal cavity cancers, or cancers of the œsophagus and larynx, as well as of the lungs, is not likely to be forthcoming. But there is the further implication of most of the authorities, that in the absence of syphilis, and in the absence of serious dental defects, smoking habits, even if carried to excess, are much less liable to produce cancers than in the presence of the conditions just mentioned. Thus Sir Bruce-Porter gives expression to the view that:

If you use tobacco in moderation, it is not going to do you any harm. Some people cannot smoke and they should leave tobacco alone. If you can prevent boys from fourteen to eighteen smoking, you will be doing a good thing, and then you can let them smoke from eighteen to eighty. Tobacco is an extraordinary comfort to a great many people, who should not be terrified from enjoying one of the few joys that remained to people of advanced years. Extremes should be avoided in either direction.

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Moderation in smoking, commenced in adult life and carried on with reasonable safeguards is, in all probability, free from serious danger, particularly in the absence of syphilis and dental impairments. If this were not so, the immense increase in cigarette smoking would unquestionably have been productive of a decided increase in cancers of the specific organs and parts most affected by smoking habits. I will review once more some of the evidence as to smoking habits which have a direct bearing upon fluctuations in the cancer death rate. Heavy pipe and cigar smoking has materially diminished during the last decade. The amount of tobacco used for smoking purposes has increased only from 228,000,000 pounds in 1919 to 231,000,000 pounds in 1928 regardless of the very substantial increase in the meantime. Consumption of chewing tobacco has materially diminished, particularly plug tobacco, from 141,000,000 pounds in 1919 to 100,000,000 in 1928. Curiously enough, however, the use of snuff has increased from 35,000,000 pounds in 1919 to 40,000,000 in 1928. Heavy cigar smoking has diminished from 7,000,000,000 in 1918 to 6,400,000,000 in 1928. Light cigar smoking has diminished from 700,000,000 in 1919 to 415,000,000 in 1928. The consumption of heavy cigarettes has diminished from 32,000,000 to 10,500,000, but the consumption of light cigarettes, or those weighing not more than three pounds per 1,000, has increased from 53,000,000,000 in 1919 to 108,000,000,000 in 1928. In other words this enormous increase in smoking habits has not been accompanied by an equal increase in tobacco consumption. The total amount consumed has increased only from 648,000,000 pounds in 1919 to 754,000,000 pounds in 1928.

Much to my regret I am unable to give absolutely trustworthy data on per capita consumption of different countries, being of the opinion that most of the published statistics fall short of intrinsic accuracy, in view of the confusion of terms. *The Norwegian International Yearbook* for 1928, for example, gives the per capita consumption of tobacco for the United States as having been 3 kilograms in 1913 and only 2.7 kilograms in 1927. But I do not think this is in strict conformity to the facts. But this consumption is the highest given for any country in the world tabulated by the Norwegian government, except Holland, which shows a per capita consumption of 3.5 kilograms in 1913 and 3.2 kilograms in 1926. Yet these two countries have by no means the highest proportionate figures for cancers of the buccal cavity, which are exceeded by those of England and Wales. Unfortunately, the tabulation does not include statistics for Cuba, which shows the highest proportion of deaths from cancer of the buccal cavity of the various countries dealt with previously, nor for Mexico City and Spain. However, the data on the subject are highly suggestive of the value of a thoroughly specialized study on the whole question which must needs profoundly affect the world's population addicted to smoking habits. In its last analysis, the actual number of persons who suffer from cancerous affections as the result of tobacco smoking is but a small proportion of those who actually practise the habit, yet the situation is sufficiently serious to demand public education along the

line of least liability, since the habit once acquired is very difficult to be gotten rid of.

The whole question of tobacco smoking as a causative factor in cancer has very recently been reviewed by Dr. Fritz Lickint, of the City Hospital of Kuckwald, Chemnitz, published in the *Proceedings of the German Society for Cancer Research*, 1929 (vol. xxx, Part 4). Doctor Lickint reviews the entire literature on the subject, quoting 167 authorities, suggestive of the vast amount of attention that has been given to the subject, but regrettably, in most cases limited to individual objective findings in a comparatively small number of cases. Lickint, however, arrives at the correct conclusion that the irritating factor of tobacco and tobacco smoking is a complex one. For aside from chemical effects, there are mechanical and caloric effects of smoking which cannot be ignored. He reports results of animal experimentations of great interest but too technical to be reviewed on this occasion. He makes one important observation and that is the absolute absence of skin cancers of the hands and fingers as the result of cigarette-smoking habits particularly in the manipulation of tobacco during manufacturing processes. According to the most recent statistics by Dublin on "The Causes of Death by Occupation," published in February, 1930, by the United States Bureau of Labor Statistics, cigar smokers and tobacco workers show a standardized relative index of cancer of 118.

Lickint confirms the observation that pipe smokers and heavy cigar smokers generally suffer most from cancer of the lower lip, which may be accepted as conclusive evidence of cause and effect. He draws attention to the practical absence of lip cancers in glass blowers and musicians using metal instruments which must involve a considerable degree of lip irritation. He includes some extremely interesting temperature observations on cigarette smoking which are also too technical to be enlarged upon but which are suggestive of a direction in which further research would be extremely valuable. He arrives at the same conclusion as Ewing that the discontinuance of smoking habits would unquestionably result in the disappearance of many of the cancers to which men at the present time are curiously liable. Lickint also endorses the view that syphilis and cancer of the tongue are in most cases closely associated and that syphilitics should absolutely discontinue smoking habits. He goes further, however, and attributes a certain proportion of deaths from cancer of the stomach to smoking habits, and of being particularly productive of ulcers of the stomach on the part of those who practise the habit of smoke inhalation. He agrees that smoking habits have a close relation to bronchial and lung cancers, attributing the increase in this form of cancer to smoking habits, particularly cigarette-smoking habits during recent years.

Summarizing the foregoing rather extended observations on one of the most important phases of the cancer problem, the following conclusions would seem admissible:

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1. Smoking habits unquestionably increase the liability to cancer of the mouth, the throat, the oesophagus, the larynx and the lungs.

2. The change in the cancer death rate during recent years has not, however, been at all disproportionate to the enormous increase in cigarette-smoking habits, which have replaced the older method of smoking, unquestionably more injurious than the smoking of cigarettes.

3. The problem is complicated by other factors, particularly syphilis and defective dental conditions, in the absence of which, smoking habits are much less likely to result in cancerous affections.

4. The increase in cancer of the lungs observed in this and many other countries, is, in all probability, to a certain extent directly traceable to the more common practice of cigarette smoking and the inhalation of cigarette smoke. The latter practice unquestionably increases the danger of cancer development.

5. In the absence of other predisposing conditions, extreme moderation in smoking habits would certainly be advisable. Likewise attention requires to be given to the use of cigarette-holders and cigar-holders of a high degree of conductivity which must needs increase the liability to cancerous affections.

6. Finally something should be said as to the gross amount of air pollution as the result of almost universal smoking habits, which may in some cases injuriously affect non-smokers who are the victims of conditions over which they have little control. This observation applies particularly to the development of cancer of the lungs which occur among women, as well as among men, and frequently among those who are not smokers.

Even the most exhaustive study of the present state of knowledge regarding smoking habits in their relation to cancer leaves many of the most important questions unanswered. There is, therefore, the utmost urgency for qualified research into what is still a rather obscure aspect of the larger problem of cancer control, and it is to be hoped that the present study will be of some aid in this direction and stimulate more qualified research workers to subject the data and conclusions to a competent analysis.

THE RÔLE OF LYMPH STASIS IN THE GENESIS OF CANCER

THE EVIDENCE OF LYMPHANGITIS IN PAPILLOMATA

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IN LAYING before my American colleagues some further evidence in favor of the view of the origin of cancer with which my name is associated, the view, namely, that cancer is a product of lymph-stasis, I desire not only to do honor to the great master of morbid histology to whom this volume is a tribute but also to give an additional proof, if such were needed, of the unexhausted possibilities of the study to which he has given his life. In the earlier part of my professional career morbid histology—in England at any rate—was regarded as *vieux jeu*, an exhausted and closed subject completely embodied in textbooks and from which nothing more could be hoped. The revival of interest in it has of late made great progress, and it is now holding its own with its younger rivals in the field of pathology such as bacteriology and bio-chemistry, and is advancing by equal steps with them. It is claiming, as much as other branches of pathology, the exclusive devotion of able young men, though in many universities and medical schools it is still inadequately recognized and endowed. It cannot be doubted that the improved position of the subject is largely due to Professor Ewing and to that great piece of organization, his work on "Neoplastic Diseases."

The evidence that cancer arises in districts where for long years there has been a local lymph-stasis, impairing the nutrition of the cells, was first stated in a paper read before the Interstate Post-graduate Convention at Cleveland in 1926.* On that occasion I was able only to state the subject in its bare outlines, and though I have returned to it since in an address given in Wellington, New Zealand, last year,† and in a recent Hunterian lecture, at present unpublished, given at the Royal College of Surgeons of England, there is still much to be said upon it. Nothing has encouraged me to pursue the subject so much as a letter received from the senior surgeon of the world, Professor W. W. Keen, in which he says, "I have just read your very interesting address on 'Lymph-stasis the Precursor of Cancer.' It appeals to me as the most reasonable and almost certain paper on the origin of cancer that I have ever seen. All others are guess work. Here is a series of facts—observations which cannot be disputed. I hope you will follow it up and be able to establish the doctrine on most solid ground. I think it gives us more nearly the origin of cancer than any other paper I have seen. Whether we can do anything to prevent or remedy the stasis of the lymph or not is the next question. If we can we can possibly prevent cancer."

* Handley, W. Sampson: Lymphatic Obstruction as a Factor in the Causation of Cancer, Transactions of Interstate Post Graduate Assembly, p. 117, Cleveland, 1926.

† Lymph-stasis the Precursor of Cancer. Brit. Med. Journ., October 5, 1929.

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Since many of the readers of this paper may not have met with my previous papers it will be necessary very briefly to restate my theory and the evidence upon which it is based. It is universally recognized that *chronic irritation* is a general, though not a universal precursor of cancer. It is necessary to use the vague word irritation because there is no specificity about the cancer-inducing irritants. They may be physical, chemical, parasitic or bacterial, and in a given area the nature of the cancer induced does not vary with the nature of the irritant employed. It has generally been thought hitherto that the irritant acts directly upon the cells which become cancerous, but no explanation or analysis of the "cancerogenic" effect has hitherto been attempted successfully. It is obviously just as likely that the effect may really be primarily an effect upon the *environment* of the future cancer cells. A study of the evidence leads directly to this conclusion, though it does not exclude the possibility of a concomitant direct irritation of the epithelial cells.

In this regard the chain of evidence is complete for one variety of cancer, namely lupus carcinoma. This is often erroneously thought to be an X-ray cancer, the result of overradiation. That this is not the case is shown by the fact that lupus cancer was fully recognized before 1895, the year in which X-rays were discovered. In a paper published in 1925* I showed that tuberculous lupus is essentially a chronic tuberculous lymphangitis of the lymphatic system of the skin. For years the epithelium in lupus plays only a passive rôle. It may be destroyed as in ulcerative lupus, but in the non-ulcerative form of lupus it gives no particular early sign of reaction.

At the edge of an area of non-ulcerative lupus the earliest change seen is that the lymphatic vessel of each papilla is replaced by a solid cord of proliferated endothelial cells. The lymphatic can easily be recognized from its position because, as I have shown, a lymphatic vessel is the axial structure around which the papilla is built.

The blocking of this central lymphatic is followed by an increase in size of the papilla both in length, and as far as the surrounding papillæ will allow, of breadth. As the section is traced from the periphery toward the centre of the area of lupus the papillæ gradually increase in length up to five or ten times the normal. In typical warty lupus (*lupus verrucosus*) the hypertrophy of the papillæ may attain an even greater degree. The appearance of cancer upon an area of old lupus is invariably preceded by such local warty thickenings of the epithelium. Having demonstrated that proliferative lymphangitis is present beyond the apparent edge of an area of non-ulcerative lupus, and that its appearance is followed by gradual papillary hypertrophy, I considered it a fair inference that the hypertrophy was a result of the lymphatic obstruction. That inference is irresistible when one considers the pathology of elephantiasis, with its great thickening of the subcutaneous tissue and its papillary hypertrophies; undoubtedly due to lymphatic obstruction.

I have thus described the effects of obstruction of a papillary lymphatic:

* Handley, W. Sampson: Lupus in its Surgical Aspects. ANNALS OF SURGERY, January, 1925.

The papilla is a little physiological engine. From its blood capillaries there exudes into its connective tissue spaces a constant nutritive stream of diluted blood plasma at a certain pressure. The excess of fluid is removed and the equilibrium maintained by the drainage action of the central lymphatic. Block this lymphatic and what will happen? The first effect will be a rise in the pressure in the intercellular spaces of the papilla, and on ordinary hydraulic principles the papilla will increase in size until the intercellular pressure is equal to the pressure in the capillary blood-vessels. A second effect will be overnutrition and consequent proliferation of the papilla itself and of the overlying epithelium. But the most important effect of all for our present purpose remains to be considered. In the normal papilla a constant stream of blood fluid, along with lymphocytes, is exuding from the capillaries and passing away by the lymphatic. As soon as the lymphatic is blocked, stasis occurs and the flow of fresh blood fluid through the papilla is arrested or greatly retarded, even though just as much blood may be passing through its blood capillaries. Two consequences are inevitable: the supply of oxygen to the tissues of the papilla, to its epithelium as well as to its connective tissue, will be much reduced; furthermore, the supply of hormones to the cells of the papilla will be cut off or greatly diminished. In this connection I use the term "hormone" perhaps somewhat loosely, to signify those products of the rest of the cells of the body which are necessary to the well-being of the cells of the papilla we are considering. Here, I think, we approach the crux of the problem.

Local lymphatic stasis brings about a definite rupture of the contract in virtue of which the unicellular organism originally forswore its egotism and became a social unit. Or, in the terms of biochemistry, the epithelium covering the papilla is deprived of the supply of growth-inhibiting substance, which in a well-conducted cell community is circulated to every cell.

I have shown that local lymphatic obstruction must seriously reduce the supply of oxygen to the epithelium of the blocked papilla. It would not be surprising if, in the course of years, the affected epithelium, adapting itself to meet this difficulty, should acquire a type of metabolism in which oxygenation played a relatively subordinate part. Warburg has recently brought forward strong evidence that the carcinoma cell, as compared with the normal epithelial cell, is an anaërobe, deriving most of its energy from the hydrolysis of sugar into lactic acid, and relatively little from oxidation. This remarkable fact is in exact accord with the theory of the origin of cancer which I am presenting to you. It must not be forgotten that in dealing with such a complex matter as the origin of cancer, direct proof is, in the earlier stages, not to be expected. All that can be hoped is to fit together the isolated facts into a coherent pattern.

In remarkable accord with the view that lymph-stasis is the great general physiological factor which lays the foundations of cancer, is the flood of evidence coming from many quarters that papilloma or adenoma is the precursor of carcinoma of every variety. This is universally the case in the occupation cancers such as sweep's and paraffin cancer, in cancer due to parasites such as gongylocoma (Fibiger) or bilharzia, in the experimental cancers due to tar or X-rays, and evidence is continually increasing that large clinical categories of cancer, such as cervical cancer (Bonney), breast cancer (Cheate and Handley), rectal cancer (Mummery and Dukes) and gastric cancer (Menetrier), are preceded by papillomata or adenomata.

If, as I maintain, the papilloma or papillary adenoma is the characteristic product of local lymphatic obstruction, we are getting near to the conclusion that all carcinomas are the result of local lymphatic obstruction. The mys-

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terious action of such varied chronic irritants all producing the same final result receives for the first time an intelligible explanation. They act by setting up a local chronic obstructive lymphangitis of the part to which they are applied, which leads after a time to the production of warts, or adenomata, and after a further interval to the genesis of a carcinoma. Congenital malformation of lymphatics, seen in moles or nævi, also produces lymph-stasis, warts and sometimes carcinoma.

Such in the baldest outline is the lymph-stasis theory of cancer. In the present paper I intend to deal with only one small branch of the subject. If papillomata are the product of obstructive lymphangitis or of lymphatic maldevelopment it should be possible in sections of warts to demonstrate the process at work, and I wish to present the evidence that such, in fact, is the case.

Common Warts.—If papillomata are due to blocking of the papillary lymphatic, an infective lymphangitis is likely to be by far the most frequent

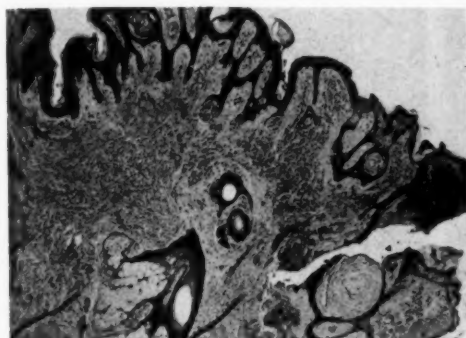


FIG. 1.— $\times 55$. Section of a melanotic wart, or warty mole from the collection of Dr. Ernest Shaw, to demonstrate the origin of lymph-stasis and papillary hypertrophy from lymphatic malformation of congenital origin.

The papillæ are greatly hypertrophied and the epithelial layer shows cell nests, but there is no malignant change. The superficial layer of the dermis—its lymphatic zone—is occupied by a richly nucleated band of nævus cells. This band shows vertical prolongations of similar tissue occupying the axis of many of the papillæ, but not quite reaching the epithelium. It is inferred that the nævus cells are derived from irregular proliferation of the lymphatic endothelium, since a lymphatic vessel normally occupies the axis of each papilla. At one point, A, in the figure, a lymphatic vessel with an open lumen is in continuity with a solid string of nævus cells.

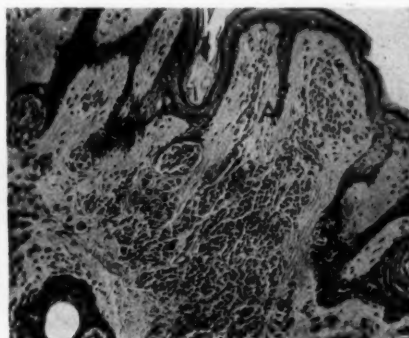


FIG. 2.— $\times 100$. A highly magnified photograph of two of the papillæ from the preceding figure. Both are occupied by axial lines of nævus cells continuous with the band of nævus cells in the superficial dermis. At A the line of nævus cells possesses a distinct lumen. This lumen and the axial position of the line of nævus cells proves its origin from the papillary lymphatic by proliferation of the lymphatic endothelium.

cause of common warts. Topley and Wilson* state that numerous workers have recorded evidence which suggests that they are infectious. Jadassohn (1896) found that they could be produced in human beings by experimental inoculation. Wile and Kingery (1921) were able to produce warts in human beings with a Berkefeld filtrate of ground-up wart material by intracutaneous inoculation. It should be noted that the successful method of infection is

* Topley and Wilson: Principles of Bacteriology and Immunity, vol. xi, p. 1247, Arnold, 1929.

identical in principle with the accepted method for artificial injection of the skin-lymphatics.

The linear arrangement frequently seen in warts of the hand suggests that, reaching the lymphatic system at one point, the infection may travel some distance along the trunk lymphatics, coming up to the surface and causing warts along the course of the infected vessel.

Borst ("Die Lehre von der Geschwulsten") emphasizes the rôle played by irritation in the causation of papilloma, so that some of them are rightly described as inflammatory, especially the warts seen on the skin and mucous membrane in the neighborhood of chronic ulcers or scars, *e.g.*, in the larynx, and in tuberculous and syphilitic affections of the intestine. Papilloma of the bladder in aniline workers is ascribed to chemical irritation, and chronic inflammation of the bladder in gonorrhœa, stone and chronic cystitis are often associated with papillomata. That developmental conditions also play a part in causation is indicated by the occasional occurrence of congenital papilloma in the bladder, the larynx and the trachea. Parasitic infections, *e.g.*, coccidiosis of the bile-ducts, may also produce papillomata. Papillomata are likely to recur after removal.

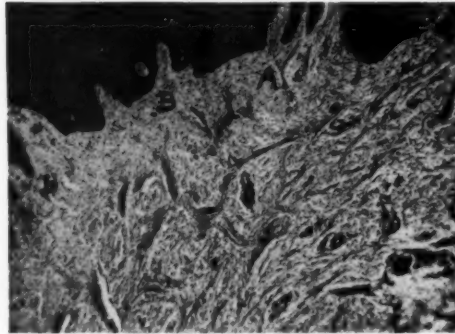


FIG. 3.—x 40. Section of an ordinary wart of the skin showing lymphangitis. Note especially at A two proliferated papillary lymphatics uniting in a characteristic Y-shaped junction. Other papillæ, BB, also show blocked central lymphatics. The dermis beneath is occupied by a reticulum of cellular lines, exactly similar to those seen in tuberculous lymphangitis. From a specimen lent by Dr. Ernest Shaw.

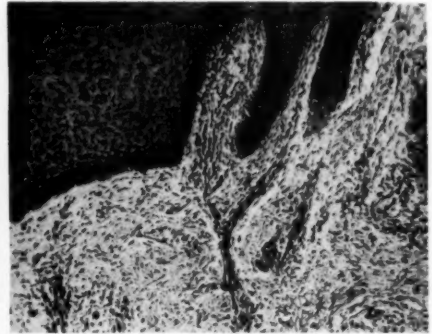


FIG. 4.—x 100 is a highly magnified portion of the preceding figure and shows the characteristic proliferative lymphangitis which has led to the blocking of the lymphatics of the papillæ. Note that the stalk of the Y-shaped lymphatic junction is directed away from the surface of the skin, a characteristic point of distinction from excretory ducts of the cutaneous glands.

Borst considers that a papilloma which becomes malignant is from its beginning malignant, but this line of argument is contradicted by innumerable clinical experiences of simple papillomata first showing malignancy after many years. The recurrence of papillomata is more simply explained as due to persistent residual infection of the lymph-vessels of the part.

Borst, in describing warts, refers to the appearances in the dermis as follows: "An inflammatory cell-infiltration of the papillæ and of the underlying connective tissue of the corium is present," but he gives no explanation of these appearances, nor any description of the peculiarities which indicate that the infiltration is due to a lymphangitis.

It is evident that if papilloma is due to obliterative lymphangitis some sections of warts should exhibit evidence of the process, though in others fibrotic processes might have obliterated the evidence. In order to investigate this question I asked my friend Dr. Ernest Shaw to allow me to inspect his collection of sections of warts and warty moles. In ten out of the eleven

LYMPHANGITIS IN PAPILLOMATA

sections available the evidence of a proliferative lymphangitis appeared quite unmistakable. Axial lines of granulation tissue were seen in the centre of the papillæ, sometimes uniting below the papillæ in a characteristic manner, and similar branching lines of granulation tissue derived from the proliferation of lymphatic endothelium, occupied the lymphatic zone, *i.e.*, the superficial third, of the dermis.

These appearances are characteristic, but the fact will perhaps not be generally admitted until histologists have become more familiar with the lymphatic arrangements of the skin. It is a remarkable fact that I have found no reference anywhere to the occurrence of lymphangitis in connection with papillomata, but anyone who looks for the association with an open mind will find it. That cutaneous moles are localized areas of congenital lymphatic malformation is the view of von Recklinghausen and other good authorities. Figs. 1 to 4 illustrate the character of the evidence of lymphatic malformation and lymphangitis found in sections of warts.

ERZEUGUNG VON BÖSARTIGEN TUMOREN DURCH EINSPRITZEN VON MILZBREI UND BLUT VON TUMORTRAGENDEN RATTEN UND MÄUSEN

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AUF der Konferenz der Leeuwenhoek-Vereinigung in Paris teilte *Fichera* mit, dass es ihm gelungen sei, mit Blut, Milzbrei und Organauszügen von Ratten und Mäusen, die mit Carcinom und Sarkom behaftet waren, wieder Geschwülste zu erzeugen, die histologisch den Geschwülsten glichen, die die Tiere hatten.

Durch diese Versuche sind die früheren Versuche von uns—Tumorerzeugung durch Milczrei von Tumortieren—bestätigt, ebenso unsere Versuche, mit Blut Geschwülste zu erzeugen, was kurze Zeit später auch Lipschütz und einem japanischen Forscher gelungen war.

Da in der Zwischenzeit von Woglom bei den Versuchen, an der Ratte mit Milzbrei von Tumortieren wieder Tumoren zu erzeugen, nur negative Resultate erzielt wurden, so haben wir unsere Versuche mit Milzbrei wieder aufgenommen.

Es ist uns auch neuerdings wiederholt bei Tumortieren, die keine sichtbaren Metastasen hatten, gelungen, Tumoren bei Ratten und Mäusen zu erzeugen, wenn wir Milzbrei von solchen Tumortieren nahmen, sowohl von Carcinom—wie Sarkomtieren. Nachdem diese Versuche von anderer Seite (*Teutschläder Tinozri, Fichera*) bestätigt wurden, dürfte wohl kein Zweifel mehr darüber bestehen, dass mit Milzbrei und Blut auch von Tumortieren (Ratten und Mäusen), die makroskopisch keine Metastasen enthalten, Geschwülste erzeugt werden können.

Immerhin bleibt der Einwand berechtigt, dass bei diesen makroskopisch metastasenfreen Tieren mikroskopisch schon Metastasen vorhanden sind, oder dass einzelne Krebszellen in den Organen und im Blut zirkulierten. Wenn man das Letztere annimmt, so hat die Frage nicht etwa, wie man meinen könnte, ihr Interesse verloren, da die Entstehung von Krebsgeschwülsten aus Krebszellen eine alte Erfahrungstatsache ist; sondern es würde dann sich darum handeln, warum eigentlich diese Entdeckung, dass mit dem Blut und dem Organbrei von Krebstieren Geschwülste erzeugt werden können, nicht schon längst gemacht wurde, sondern im Gegenteil dies bisher als nicht möglich galt, worauf *Fichera* in Paris besonders hinwies.

Wir haben alle Mühe, mit Geschwulstbrei Tumoren zu erzeugen, wenn wir bei der Stückchen-Impfmethode nicht genügend grosse Stücke nehmen bzw. eine genügende Menge Geschwulstbrei einspritzen. Selbst für das Rous-Sarkom hat Ernst *Fränkel* nachgewiesen, dass man nicht unter eine gewisse Anzahl von Zellen heruntergehen darf, damit das Angehen von

ERZEUGUNG VON BÖSARTIGEN TUMOREN

Tumoren mit Zellen gelingt. Unsere Milzbrei und Blut versuche würden also, wenn man das positive Ergebniss auf wenige vorhandene Krebszellen zurückführen wollte bedeuten, dass Krebszellen in der Milz und im Blut in ganz minimaler Menge imstande sind, Krebs zu erzeugen, d.h. dass also die Krebszelle in der Zirkulation weit virulenter ist als im Tumor selbst. Ferner hätten diese Versuche gezeigt, dass, wenn wir die Tumorbildung auf das Vorhandensein von Krebszellen zurückführen, wir damit rechnen können, dass auch beim Menschen Zellen im Blute zirkulieren zu einer Zeit, wo wir klinisch nichts von Metastasen nachweisen können. Und es entsteht nunmehr die dringende Frage, ob solche Krebszellen nicht beim Menschen schon im Frühstadium in der Zirkulation vorhanden sind und ebenfalls virulenter sind als die Krebszellen im Tumor selbst.

Die Entscheidung dieser Frage ist umso brennender, als, wie wir gesehen haben, ja gerade solche zirkulierenden Krebszellen besonders fähig zur Tumorbildung zu sein scheinen. Es entstehen also auch für den Fall, dass wir nur zirkulierende Krebszellen im Blut und im Gewebe nachgewiesen haben, wo wir sie bisher nicht vermuteten, neue wichtige Probleme, die wir noch genauer erforschen müssen.

Andererseits aber sprechen unsere positiven Impfungen mit menschlicher Krebslymphe (Lymph, Exsudat) an der Ratte gegen die Deutung, dass nur dann eine Uebertragung möglich ist, wenn Zellen im Blute sind, da es sich um Tumorzellen einer anderen Spezies handelte.

Es bleibt die Frage also offen, ob es überhaupt die Krebszelle ist, welche in diesem Falle die karzinogenen Eigenschaften ausübt, und ob nicht vielmehr ein Krebsagens, wie beim Rous-Sarkom, die tumorbildenden Eigenschaften in der Zirkulation ausübt, und dass das Auffinden einzelner Krebszellen nur ein nebensächlicher Befund ist, da diese für die Krebsbildung nicht in Frage zu kommen brauchen.

Bei unseren Arbeiten, mit Blut Tumoren zu erzeugen, haben wir uns auch mit der Frage beschäftigt, wie sich das Blut von Spontantumortieren verhält. Bekanntlich sind Spontantumoren sehr schlecht übertragbar, und wir hatten auch neulich wieder einen Spontantumor bei einer Maus an der Brust, der ebenfalls bei der Uebertragung anfangs sich bildende kleine Tumoren hervorrief, die später aber zurückgingen. Es war nun interessant, dass es mit dem Blute dieses Tieres gelang, unter 10 Tieren 2mal Tumoren zu erzeugen, die weiter wüchsen und den Tod der Tiere zur Folge hatten und transplantabel waren.

Es entstand weiter die Frage, an welche Elemente des Blutes die kanzerogenen Faktoren geknüpft sind. Wir haben schon in unserer ersten Arbeit mitgeteilt, dass es fast nie gelingt, mit dem Serum Tumoren zu bekommen. Wir nehmen jetzt das Blut aus den Axillargefäßen, reiben das z.T. geronnene Blut sofort mit Kochsalzlösung an und spritzen es wieder ein. Jeder Versuch, das wirksame Prinzip von der Blutkörperchen zu isolieren, scheiterte. Es konnte immer nur dort gefunden werden, wo die Blutkörperchen waren.

Wir haben dann weiter versucht, ob es nicht möglich sei, das angenommene Krebsagens von der Krebsgeschwulst auf die Blutkörperchen zu übertragen. *Auler* hat Geschwülste mit Kochsalzlösung zu einem Brei verrieben, dann diesen stark verdünnten Geschwulstbrei scharf zentrifugiert, sodass die darüberstehende Flüssigkeit bei der Einspritzung keine Tumoren mehr gab, Setzte man nun dieser Flüssigkeit Blutkörperchen hinzu, die aus normalem Blut isoliert waren und spritzte sie Versuchstieren derselben Art, Mäusen oder Ratten, ein, so entwickelten sich dieselben Tumoren wie der Tumor, aus dem der wässrige Auszug gemacht war. Diese Resultate waren allerdings nur positiv bei dem Mäusesarkom S.37 und bei dem Rattensarkom Jensen; sie waren immer negativ bei dem Ehrlich-Carcinom und bei dem Flexner-Jobling-Carcinom.

Während dieser Versuche kam *Auler* auf die Idee, dem Jentsentumor (Rattensarkom) Blutkörperchen von einer normalen Maus hinzuzufügen und das Gemisch Mäusen einzuspritzen. Die bei den Mäusen entstandenen Tumoren konnten dreimal unter fünf erzeugten Tumoren auf Mäuse weiter übertragen werden, schon bis zur vierten Generation. Nur ganz im Anfang waren sie noch auf Ratten zurück übertragbar; wenn sie dagegen eine gewisse Grösse erreicht hatten oder von der zweiten Generation ab, konnten sie nicht mehr auf Ratten zurück übertragen werden. Auch diese Versuche gelangen nur bei dem Mäusetumor S.37 und bei dem Jensen-Sarkom, bei dem Ehrlich-Mäusecarcinom und bei dem Flexner-Jobling-Rattencarcinom gelangen diese Versuche nicht.

Die Histologie der fünf erzeugten Tumoren enthält in allen Fällen der ursprünglichen Tumorart, d.h. es wurden immer Sarkome erzeugt; in drei Fällen waren es Spindelzellensarkome, in zwei Fällen bildeten sich dagegen Tumoren, welche mehr den Charakter von Endotheliomen hatten.

MULTIPLE MYELOMA

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THE chief purpose in presenting this paper is not so much to report additional cases of a comparatively rare disease, but to try to throw some light upon the problem of treatment.

That multiple myeloma is always fatal, and that no treatment is known of any value even in checking the progress of the disease, has been so universally accepted that the question of treatment is scarcely referred to in the very considerable literature on the subject.

According to Ewing¹ these cases invariably have a fatal termination. But that multiple myeloma is, in most cases, highly sensitive to both the toxins of erysipelas and *Bacillus prodigiosus* and to radiation, is, I believe, definitely established. Furthermore, the inhibitory action of these two agents is not only sufficient to cause great amelioration of the symptoms—in most cases but the disappearance of the tumors, in a few cases with apparently, a lasting cure of the disease.

The most important case of our series is that of Dr. J. J. Thomas of Boston.² Although published in the *Boston Medical and Surgical Journal* in 1901, and referred to in my publication of 1913,³ its real significance has never been recognized because the later history of the case has never been recorded in detail. It is a clear-cut case with the diagnosis well established by clinical and microscopical evidence. What makes it unique is the later history. At the time of Thomas' report, only a few months had elapsed since the operation and the appearance of rapidly developing metastases to the ribs. It was stated that the patient was taking Coley's toxins, and had shown improvement. As a matter of fact, the improvement continued. The toxin treatment was kept up, twice a week, for two years, under my direction. The patient made a complete recovery, and remained well for five years when he died of acute lobar pneumonia.

So far as is known, this is the only case on record of a multiple myeloma that has recovered under any form of treatment, and the patient remained alive for five years, except the Gilmore case in which there was a difference of opinion in regard to the diagnosis.

The Marine Hospital case of multiple metastatic myelosarcoma with extensive involvement of the bones and soft parts, reported by Christian and Palmer⁴ is, in my opinion, a case of probable multiple myeloma primary in the tibia (see Case XIV). The microscopical diagnosis of Dr. Ewing Taylor was that of myelosarcoma concurred in by Doctors Ewing and Codman. Amputation at the thigh was performed in September, 1925. Three months later extensive multiple metastases developed in the stump, inguinal glands, clavicles, skull, abdominal wall and elsewhere. All disappeared under prolonged toxin treatment, without radiation or other treatment; the patient regained his lost weight of forty pounds and has remained in good health without evidence of a recurrence, up to the present time, more than four and one-half years since the beginning of treatment.*

* Doctor Wood states that microscopically it is a metastatic carcinoma. Diagnosis of multiple myeloma was made by Doctor McWhorter.

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As further evidence of the inhibitory action of the toxins combined with irradiation, I might cite the case of Mrs. C. (see Case V) which is briefly as follows:

A female, aged forty-four years, was brought to the Memorial Hospital in November, 1928, from a home for incurables, after her condition had been pronounced hopeless by Dr. Howard Lilienthal. On examination I found a large tumor involving the upper third of the femur, with a pathological fracture; the disease invaded the sacrum; there was



FIG. 1.—Case V. Plasma-cell myeloma of femur and spine.

paraplegia, and considerable loss of weight. I agreed with Doctor Lilienthal that the condition was hopeless. At the urgent request of the patient's husband I consented to give her a brief course of toxin treatment and irradiation. The toxins alone were used at first, with marked improvement; at the end of three weeks, one radium pack was applied, with rapid and continuous improvement. In this case the original diagnosis of Doctor Ewing was that of endothelial myeloma, and the case was reported as such by Coley and Coley.⁶ On reviewing the sections, recently, Doctor Ewing and Doctor Stewart, of the Memorial Hospital laboratory, have concluded that the case should be

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classified as a plasma-cell myeloma. (Fig. 2.) No radiation had been applied to the spinal tumor, this tumor apparently disappearing under toxins alone as the patient completely recovered from the paraplegia and had no return of it up to the time of her death, two years later, from metastases to the brain. I think there is every reason for believing that the result in this case might have been different had the toxin treatment been kept up for a longer period of time instead of being discontinued at the end of five months.

In another case of plasma-cell myeloma, an apparent recovery has followed the use of irradiation when applied at the Memorial Hospital under the direction of Doctor Stone and Doctor Herendeen.



FIG. 2.—Case V. Plasma-cell myeloma.

L. C., female, aged fifty-two years, was admitted to the Memorial Hospital in August, 1926, with a history of having had shooting pains in her right leg for nearly three years. A röntgenographic diagnosis of osteitis fibrosa cystica, or giant-cell sarcoma, had been made. A biopsy was performed, revealing a tumor, the structure of which was typical of plasma-cell myeloma. Under irradiation at the Memorial Hospital she showed remarkable improvement, with almost complete restoration of function. When last heard from, more than three years later, she was able to get about comfortably, and was, apparently, free from all evidence of the disease.

In another case, beginning as a solitary plasma-cell myeloma, the disease was almost completely controlled by radium-pack treatment, the patient remaining well for two years (see Case VI).

J. K., male, aged fifty-eight years, whose first symptoms, pain and soreness around the greater trochanter, appeared in December, 1923. Numerous diagnoses were made from the clinical and röntgenographic evidence. Biopsy revealed a typical plasma-cell

myeloma. There was a pathological fracture. The radium pack was applied by Doctor Stone, over three different areas. The patient remained well for two years when he developed multiple metastases; the disease progressed rapidly, causing death in a short time.

Here, again, there can be no question of the value of irradiation in a case of definitely proven multiple myeloma. I believe if this treatment had been continued, supplemented by systemic toxins, it is not improbable that the disease might have been held under control for a longer period of time, possibly permanently.

Frequency.—Multiple myeloma is a very rare disease. When Thomas reported his case before the American Neurological Association in 1901, he was able to find only nineteen cases in medical literature. In 1920 there were only 118 cases on record. The number has increased more rapidly in recent years, owing, in part, to the steadily growing interest in the study of bone tumors. Geschickter and Copeland, in their publication of 1928, in addition to describing the thirteen cases observed at the Johns Hopkins Hospital since it was founded, called attention to 425 additional cases that they had been able to find in the medical literature up to 1927, and they have included in their paper a most valuable bibliography, giving the reference to these cases in the order of publication.

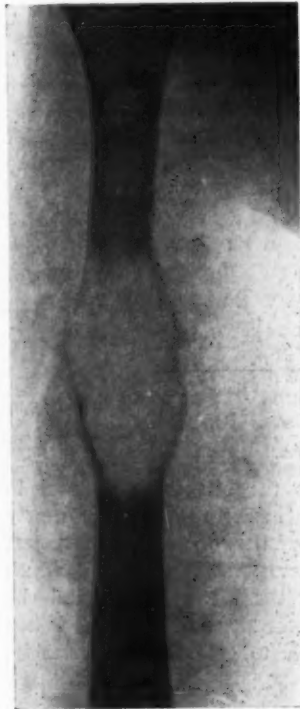


FIG. 3.—Solitary plasma-cell myeloma before treatment.

Onset.—Multiple myeloma in most cases begins with a fairly characteristic onset, without any known predisposing cause unless it be local trauma, which has been observed in about 20 per cent. of the cases. The patient complains of severe localized pain. The pain is usually intermittent in character, greatly aggravated by motion, and disappearing when the body or limb is at complete rest. This pain continues to increase in severity and is usually treated for neuritis of one of the long bones, for lumbago, or for rheumatism if in the spine. Loss of weight and anæmia often follow quickly.

Clinical Appearance.—Multiple myeloma has certain very definite clinical characteristics which enable one to make a diagnosis in the majority of cases. These characteristics may be described as follows:

1. *Tumor.*—A tumor originating in the cancellous portion or in the marrow of a bone.
2. *Site.*—Multiple myeloma has a predilection for certain bones, and the bones most often affected in the early stages of the disease are: the ribs, spine, humerus, femur, knee and pelvis. In our own series the disease was first noticed in the following bones: humerus, 2;

MULTIPLE MYELOMA

femur, 4; tibia, 2; spine and ribs, 3; ribs, 1; ribs and skull, 1; ilium and tibia, 1; clavicle and ribs, 1.

In three cases a diagnosis of solitary plasma-cell myeloma was made.

3. *Multiple Involvement*.—While this may not be observed in the early stages of the disease, multiple foci are soon discovered which may have existed from the very beginning.
4. *Pathological Fracture*.—The lesions are characterized by bone destruction with a complete absence of new bone formation. This destructive process proceeds rapidly so that in many instances a pathological fracture may occur within two or three weeks of the first symptom (localized pain).

In our own series, a pathological fracture was observed in 50 per cent. of the cases. This is slightly higher than has been found in any other form of bone neoplasm.⁶ In the Johns Hopkins series, a pathological fracture was noted in 62 per cent. of the cases.

5. *Paraplegia*.—Early paraplegia occurs in cases in which the spine is involved. In these cases we may find a distinct kyphosis (observed in two of our cases). There may be varying stages of scoliosis or lordosis, and even a marked shortening of the spine due to disintegration and collapse of the vertebra. Paraplegia was noticed in 40 per cent. of our own series. The disease develops very slowly. It is characterized first by weakness in the legs, increasing difficulty in urinating, Babinski's sign, and finally, definite paraplegia.
6. *Bence-Jones Bodies*.—The presence of Bence-Jones bodies has been observed in about 8 per cent. of all cases. While this condition may be associated with other diseases, it is of great diagnostic significance in multiple myeloma, especially in the presence of multiple lesions of bone with the clinical and röntgenographic features of multiple myeloma.
7. *Nephritis*.—While changes in the kidney were noticed in 70 per cent. of the Johns Hopkins series, chronic nephritis has not, by any means, been constant in our own series.
8. *Backache*.—Severe backache is always present in cases in which the spine is involved, but in other cases localized pain, greatly exaggerated by muscular strain, is the first symptom.

Röntgenographic Appearance.—The röntgen-ray will usually reveal features which, while not absolutely pathognomonic, still point strongly to a diagnosis of multiple myeloma. These features include sharply localized areas of bone destruction in a number of different bones. They often have a "punched out" appearance. If the ribs are involved, there may be a large number of areas of destruction giving a distinct mottled appearance. The bones most frequently affected are the ribs, the spine, the skull, and, less often, the long bones.

If the disease starts in one of the long bones, first as a solitary lesion, a plasma-cell myeloma, the röntgenogram may closely resemble that of an endothelial myeloma. This resemblance applies to the microscopic picture as well.

Clinical Course.—The clinical course depends much upon the locality of the disease, in other words, upon the bones affected. The solitary plasma-cell myeloma which, in some cases, especially those of the humerus, closely resembles a cyst or a giant-cell tumor, cannot be differentiated from an endothelial myeloma. In these cases, early pathological fracture is the rule. According to Geschickter and Copeland, 60 per cent. show a thoracic deformity, often being mistaken for Paget's disease or osteitis fibrosa cystica generalized. In thoracic involvement, the region on either side of the sternum and the clavicles are favorite sites. While the tumors may be palpable, they are nearly always small and only slightly raised above the normal surface of the bone. The tumors of the ribs and skull are soft and resilient and so highly vascular that pulsation often is easily detected.

A brief analysis of the following four series is of interest.

*Meyerding's*⁷ Series of thirteen cases treated at the Mayo Clinic: males, 9; females, 3; sex not stated, 1. Ages ranged from forty-three to sixty-nine years. Duration of disease extended from three months to four years. Microscopical examination made in 4 cases. Trauma noted in 4 cases (indefinite in 1 case). Locality of disease: skull, 4; ribs, 5; humerus, 2; spine, 4; femur, 2.

*Thomas's*⁸ Series of eighteen cases collected in 1901: males, 12; females, 4; sex not stated, 2. Ages ranged from thirty-six to eighty years. Duration of disease extended from two months to seven years. Microscopical examination made in 13 cases. Locality of disease: ribs, 11; spine, 6; humerus, 2; skull, 3; clavicle, 2.

Geschickter and Copeland's Series of thirteen cases observed at the Johns Hopkins Hospital: males, 9; females, 4. Ages ranged from thirty-seven to seventy-two years. Microscopical examination made in 11 cases.

Personal Series of sixteen cases: males, 12; females, 4. Ages ranged from sixteen to sixty-eight years. Microscopical examination made in 11 cases. Trauma noted in 7 cases.

Thomas found the presence of albumose in the urine in eleven of the nineteen cases of undoubted myeloma. He states that while this is by no means constant, it is certainly present in more than traces in a majority of the cases, and its presence is always enough to direct our attention to the possibility of disease of the bones, and may lead to a correct diagnosis.

Etiology.—In regard to the etiology of multiple myeloma we know just as little about it as we do about that of malignant tumors in general. Like carcinoma it is found chiefly in middle life. Eighty per cent. of the cases thus far observed have occurred between the ages of forty and seventy years. Geschickter and Copeland state that only 5 cases were found under the age of thirty-five years, and in two of these the diagnosis rested on clinical and röntgenographic evidence. One of our cases occurred in a youth aged seven-

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teen years, and Gillespie, of Fort Worth, Texas, has reported a case in a child aged eighteen months.

The finding of early multiple foci of disease in widely separate bones suggests the possibility or probability that we are dealing with a constitutional disease in which the causative agent is present in the circulation and finds a foothold in the marrow of certain bones where, by reason of impaired circulation or local trauma, it finds a favorable site for development.

Multiple myeloma resembles endothelial myeloma or Ewing's sarcoma so closely that it cannot always be differentiated by the clinical and röntgenographic evidence; and in a few cases the microscopic picture of the two conditions has been found to be strikingly similar. The age incidence, however, is somewhat different, endothelial myeloma occurring frequently in childhood or youth, whereas multiple myeloma is seldom found under the age of forty years.

These two conditions, we believe, furnish strong evidence in support of an extrinsic or infectious origin, and the occasional marked rise in temperature further supports this view. While some writers would explain this rise of temperature as being due to intercurrent infections, we believe it more probably due to degeneration and necrosis of certain areas of very rapidly growing tumors of bone, with the consequent absorption of the products of degeneration. We have observed a case of very rapidly growing tumor of the upper end of the humerus in a boy aged five years, which, in spite of heavy Röntgen therapy, grew to the size of his head within three months. A diagnosis of endothelial myeloma was made. In this case the temperature would rise for a week at a time to 103° or 104° daily, and would then subside, later rising. There was never any evidence of infection in this case. In one of our most recent cases of multiple myeloma (ilium, femur and tibia) in a young man aged seventeen years, in which the disease developed very rapidly, the temperature rose to 103° or 104° daily for weeks. The whole course of the disease was a little over three months.

If we accept the theory that all types of sarcoma, including endothelial myeloma and multiple myeloma, are due to some unknown extrinsic agent or virus, then the close similarity of these cases to osteomyelitis or inflammatory condition of bone is easily explained, and the problem then would be to differentiate two groups of tumors, *i.e.*, (1) those tumors that are now regarded as inflammatory, due to certain known micro-organisms or infectious agents; and (2) those due to some infectious agent which, up to the present time, has never been discovered or definitely classified. Until we have further knowledge, there is little to be gained by a further discussion of the etiology.

Gross Anatomy.—This has been best described by Ewing in his textbook on "Neoplastic Diseases" (1928). To quote him:

"The tumors are soft or firm, translucent or opaque, and whitish, gray, or deep red according to vascularity. Hæmorrhage, infarction, blood cysts, and necrotic areas may be present. The bone tissue suffers active absorption and the shafts become very thin,

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or multiple perforations result, or fractures occur. After passing the periosteum the surrounding tissues are diffusely invaded.

"Many cases terminate without metastases in the organs, but distant secondary growths have been found in the liver, spleen, kidney, lung, and ovary, while in certain very malignant cases, that probably belong in this category, nearly every organ in the body may be involved."

"While in some cases the cells of myeloma exhibit the features of plasma-cells, large or small with a single or multiple nuclei, yet in the entire scope of tumors which prob-



FIG. 4.—Case VII. Solitary plasma-cell myeloma of femur.

ably belong in this class the cells vary widely in size and character. In some cases the entire tumor is composed of loosely packed typical plasma-cells, 8 to 12 in diameter, round, oval, or polygonal, and with opaque, amphophile, non-granular cytoplasm. The single or multiple nuclei are relatively small, eccentric, or protruding from the cytoplasm, surrounded by a clear zone, and presenting blocks of chromatin arranged along the nuclear membrane. Mitotic figures are observed in many cases, but are less numerous when the cells are typical plasma-cells. Certain cytoplasmic bodies have been interpreted as centrosomes (Christian). The clear zone about the nucleus has been described as a vacuolated secretory product. In rare cases the round cells are mingled with spindle cells which probably result from pressure (Wieland).

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"In a second group of cases the cells are larger, giant cells with multilobed nuclei appear, multiple and vesicular nuclei are more prominent, nucleoli are large and acidophile, the resemblance to plasma-cells is not striking, the tumors are more malignant and metastases occur. Here one finds a structure which recalls lymphosarcoma with large cells. . . .

"Bone trabeculae undergo simple absorption, or, in the case of compact bone, osteoblasts are found in lacunae. The tumor never produces bone. An inflammatory reaction with exudate of lymphocytes and plasma-cells may mark the advance in bone marrow, periosteum, or other tissue."

Histogenesis.—"That the tumor cells in one group of cases represent various forms of plasma-cells," states Ewing, "is strongly attested by the comparison made by Christian. In one group of cases the identity with plasma-cells is so striking as to suggest that those writers who doubt this identity have never seen such a case."

"In another group of cases the cells lack close resemblance to plasma-cells, and their form and arrangement strongly suggest an origin from the blood-forming cells of the marrow."

"Thus if one classes myeloma according to the views of different observers concerning the origin of the tumor-cells, the following groups appear: (1) Plasmocytoma, (2) erythroblastoma, (3) myelocytoma, adult and embryonal, (4) lymphocytoma. Whether such varied interests are actually represented in the scope of multiple myeloma, or whether we have to deal with varying grades of anaplasia in a single cell of origin remains to be determined. At present the data seem to favor the former alternative."

Recent writers, especially Geschickter and Copeland, do not attempt to distinguish between the many different varieties based upon the morphological characteristics, but include them all in two groups, *i.e.*, (1) plasma-cell and (2) myelocytic type, and they claim that it is not always possible to differentiate these two. They have repeatedly observed cases in which authorities who have examined the same sections have differed between the two terms.

Differential Diagnosis.—The clinical features of multiple myeloma have already been described. The condition most likely to simulate it is endothelial myeloma. In both conditions the disease, if not multiple when first observed, soon shows multiple lesions. In both, the trouble starts in the marrow of the bone and destroys the adjacent bone. In multiple myeloma this destructive process is less widespread, seldom involving any great length of the shaft of a long bone, but confining itself to a limited area of bone-destruction, and causing an early pathological fracture. This condition is much more highly vascular and often shows distinct pulsation. In the ribs, early fracture gives rise to crepitus on palpation, and marked pain on deep inspiration or movement of the ribs.

While the roentgenogram of multiple myeloma (solitary type) of a long bone may resemble closely that of a giant-cell tumor, the location usually is quite different. The giant-cell tumor in most cases is found near the epiphysis of the bone while the multiple myeloma is in the shaft.

Then, again, the course of the disease is much more rapid in multiple myeloma and pathological fracture occurs more quickly. Furthermore, the pain in multiple myeloma is much more severe.

Another condition that may be mistaken for multiple myeloma is metasta-

tic carcinoma. The röntgenogram may simulate a multiple myeloma so closely that it is impossible to differentiate it, and the diagnosis may not be possible until a microscopic section has been examined or an autopsy performed. Two years ago there was such a case observed at the Memorial Hospital.

Solitary Plasma-cell Myeloma.—Only one example of solitary plasma-cell myeloma was found in the first thousand cases of bone sarcoma recorded in the Bone Sarcoma Registry. We have had two examples of this type of myeloma at the Memorial Hospital during the last four years. One occurred in a male aged forty-eight years, and the other in a female aged fifty-two years. In one the disease originated in the mid-shaft of the humerus, and in the other, in the upper end of the femur. In the humerus case the disease at first showed signs of regression, but a pathological fracture developed which showed no tendency to unite in spite of heavy radiation and toxin treatment. Amputation was performed, and the patient is well at present, about six months later. The femur case responded well to radiation, and the patient is in good health at the present time, more than three years later.

Metastatic Carcinoma.—In making a differential diagnosis between multiple myeloma and metastatic carcinoma one should bear in mind that Bence-Jones protein is rarely found in metastatic carcinoma, and that while the two conditions are apt to occur in similar bones, multiple myeloma usually involves the flat bones while metastatic carcinoma, particularly the breast cases, is more often found in the long bones, especially in the femur. A carcinoma of the prostate most frequently metastasizes to the bones of the pelvis or the lower spine. Then again, the multiplicity of lesions is usually a much more prominent feature in multiple myeloma than in metastatic carcinoma. The röntgenographic appearances of the tumor may be of help in making a diagnosis: In metastatic carcinoma of the prostate, there is a certain amount of bone production while in multiple myeloma the process is always one of bone destruction.

Fibrocystic Disease.—This condition may in certain cases resemble multiple myeloma, but the locality of the tumor should render the diagnosis comparatively easy. Fibrocystic disease is most frequently found in the long bones while multiple myeloma is found chiefly in the flat bones.

The greatest difficulty will be encountered in making a diagnosis between solitary plasma-cell myeloma, metastatic carcinoma and giant-cell tumor. However, in cases of doubt, the clinical history, the multiplicity of lesions, the bones involved, and the presence or absence of Bence-Jones Bodies, will be of a great diagnostic value.

Metastases.—Most writers have stated that multiple myeloma never metastasizes in the lymph-glands or in the viscera, but is found only in bones, preferably the flat bones. While this is true in a general way, there have been a number of cases reported in which visceral metastases have been observed.

In a paper on "The Multiple Myelomata and Their Ability to Metasta-

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size,"⁹ Symmers reports two cases from the Pathological Department of Bellevue Hospital. It is worthy of note that since the establishment of the Pathological Laboratories of Bellevue Hospital twelve years previously, only eight cases of multiple myeloma were encountered in 6000 autopsies.

Symmers believes that in embryonal life "the liver and spleen are hæmopoietic organs auxiliary to the bone-marrow, but in extra-uterine life the marrow assumes the task of hæmatogenesis to the exclusion of the liver and spleen." Under certain conditions, he states, it may be possible for this blood-forming function of the liver and spleen, which was lost at birth, to be reawakened. He regards his second case, as one reported by Christian, in which there were secondary neoplastic nodules in the soft parts of the arm and axilla, as representing the only really indisputable examples of genuine metastatic myelomata to be recorded. Both of them effectually violate the generally accepted dictum that the myelomata do not metastasize by cell transplantation.

Multiple Myeloma in Early Life.—Nearly all writers state that multiple myeloma is never found under the age of thirty years, and this statement is subscribed to by Geschickter and Copeland in their recent paper on the subject. Our own series contains one case of rapidly progressing disease in a boy aged seventeen years, and Gilmore,¹⁰ of Fort Worth, Texas, reports a case occurring in a child aged eighteen months when the first symptom appeared. Because of the extreme youth of the patient, this case has not been accepted by some pathologists as a true multiple myeloma.

While in this case six pathologists of the Bone Sarcoma Registry committee each gave a different diagnosis, in the opinion of Dr. Francis Carter Wood it was a multiple myeloma. The clinical history of destructive lesions of many bones, the extreme sensitivity to radiation, the Bence-Jones protein in the urine, all point strongly to a diagnosis of multiple myeloma. If this case, strictly speaking, does not belong to this group, it certainly comes under that of endothelial myeloma or Ewing's sarcoma with very wide generalization, and becomes the first case on record of an endothelioma with wide generalization that has been cured by radiation alone, and the patient well for five years.

SUMMARY OF RESULTS OF TREATMENT IN THE CASES WHICH FORM THE BASIS OF THE PRESENT REPORT

There were three cases treated with the mixed toxins of erysipelas and *Bacillus prodigiosus* alone, *i.e.*:

CASE I.—(Doctor Thomas' case.) The disease involved the spine and ribs after incomplete operation on the spine. The patient recovered, and remained well for five years, when he died of pneumonia.

CASE XIV.—(Marine Hospital case.) After amputation of the tibia in September, 1925, multiple metastases developed in skull, clavicle, femur and soft parts. The patient made a complete recovery and regained forty pounds of lost weight. He is in excellent health at the present time, with no evidence of a recurrence four and one half years later.

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CASE XII.—Was treated with toxins for a few weeks, with little apparent effect. The patient lived out of town and the treatment was not pushed to the point of producing severe reactions. New lesions developed rapidly in the ribs and spine, and treatment was abandoned.

There were eight cases treated by toxins and radiation, as follows:

CASE V.—Involving the femur and spine (paraplegia and pathological fracture of femur when the treatment was begun). (Figs. 1 and 2.) One radium-pack treatment was given to the femur; none to the spine. The toxins were kept up for four to five months. The patient made a complete recovery; the paraplegia disappeared and the fracture united. She remained well for two years and then died of metastasis to the brain.

CASE IX.—Plasma-cell myeloma, solitary, of the humerus treated with radiation and toxins. There was little change in the size of the tumor. A pathological fracture occurred and showed no tendency to unite. Amputation was performed, followed by further toxin treatment. The patient is well six months later.

CASE III.—Involving the spine and ribs. Treated by toxins and Röntgen-ray with marked temporary improvement. After six months it was impossible to hold the disease in check and the patient died shortly afterwards.

CASE XI.—Involving the ribs and skull; treated with toxins and radium. Marked improvement has been noticed. The toxin treatment has been continued at home and the patient is able to carry on his occupation. This is a recent case.

CASE XIII.—(Treated by Doctor Bloodgood.) Involving the femur, with pathological fracture. Under eighteen doses of toxins marked improvement was noticed with reunion of fracture. The bone was refractured from walking too soon without proper support. Patient is now taking Röntgen-ray therapy. The bone is again reuniting, and there is little, if any, evidence of the disease remaining. This is a recent case.

CASE X.—Involving the humerus; pathological fracture. Under toxins and radium the bone united. Three months later another lesion developed in the clavicle; another fracture. Recovery under treatment. Three months later the disease recurred in two ribs. This disappeared under similar treatment. Three months later the other humerus became involved; recovery under treatment. Three months later the dorsal spine became involved; recovery under treatment. Fifteen months later a lesion appeared in the cervical spine. Died June, 1930.

CASE VIII.—Involving the spine and ribs. The disease was held under control for four years by Röntgen-ray; it later metastasized to two ribs; was not controlled by further radiation; greatly steadily. The patient developed complete paraplegia with paralysis of the vocal cord; had lost fifty-six pounds in weight, and was confined to bed when the toxin treatment was begun (August, 1928). A complete recovery took place (with exception of bladder of which he lost control in 1924 at the time of the original operation) and he is in good health with no evidence of disease, nearly two years and four months later.

There were four cases treated by radiation alone, as follows:

CASE VI.—Involving the femur. The patient remained well for two years and then developed multiple metastases causing death in a few months.

CASE XVI.—Involving the clavicle. Excision followed by radiation. Temporary improvement; death in one and a half years.

CASE XV.—Involving the tibia. Marked improvement under radiation. Disease held in check for one year.

CASE VII.—Involving the femur (solitary). (Fig. 4.) Complete control under Röntgen therapy. Patient well more than three years later.

In two other cases, II and IV, the disease was so far advanced that, while toxins were given for a very short period, nothing was to be hoped

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for by treatment; nearly every bone was involved. In a recent case, primary in the ilium, in a young man aged seventeen years, the patient had been taking small doses of toxins for about two weeks in conjunction with Röntgen therapy. He was running a temperature of 104° daily and was profoundly ill. Röntgenograms showed both femurs and tibiae to be involved. Death occurred in about three months.

We believe that the results obtained in this series fully justify our opinion that the prognosis in multiple myeloma is not always fatal; and that if the method of treatment herein described is employed (toxins of erysipelas and *B. prodigiosus* combined with irradiation) marked improvement with control of the intense pain may be looked for in most cases. In a certain number, complete control of the disease and a permanent cure may be effected.

CONCLUSIONS

1. The prognosis in multiple myeloma is by no means so hopeless as is universally believed.
2. Most cases of multiple myeloma of both the ordinary and the solitary varieties are extremely sensitive to both the toxins of erysipelas and *B. prodigiosus* and to radiation.
3. In a number of cases the disease has been held in check for a very considerable period of time by the toxins alone or radiation alone, or by a combination of both agents.
4. In four cases, two treated by toxins alone, one by toxins and radiation, and one by radiation alone, respectively, the disease has apparently been eradicated, and the patient has remained well for a sufficient length of time to justify the hope of a permanent cure.
5. No case of multiple myeloma should be given up as hopeless without a prolonged trial of both toxins and radiation.

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LA MÉTAPLASIE ÉPITHÉLIALE ET SES RAPPORTS AVEC LES TUMEURS

PAR G. ROUSSY AND CH. OBERLING

DE PARIS, FRANCE

L'EXISTENCE de tumeurs hétérotopiques telles que les épithéliomas malpighiens dans le domaine des muqueuses cylindriques est connue depuis fort longtemps. L'interprétation de ces faits a suscité de nombreuses discussions; les hypothèses multiples émises à ce sujet se ramènent essentiellement aux deux suivantes: l'une admet une malformation embryonnaire, l'autre, une métaplasie malpighienne de la muqueuse cylindrique.

Or, depuis que la possibilité d'une telle métaplasie a été indiscutablement démontrée, la deuxième hypothèse a nettement gagné du terrain, et, puisque la métaplasie, elle-même, semble conditionnée par des processus inflammatoires chroniques on n'a pas manqué d'insister sur les relations très étroites qui se révèlent ainsi entre les processus irritatifs chroniques, la métaplasie et les tumeurs. Les adeptes de la théorie irritative du cancer ont donc tiré de la métaplasie un argument apparemment très démonstratif en faveur de leur conception; Ménétrier par exemple affirme que "l'intérêt de ces faits est considérable au point de vue de la pathogénie du cancer puisque toutes ces modifications de l'épithélium sont suscitées par des irritations, des inflammations chroniques qui se montrent ainsi génératrices du processus cancéreux."

Mais en étudiant de plus près les rapports qui existent entre l'irritation chronique et la métaplasie d'une part, entre la métaplasie et les tumeurs hétérotopiques d'autre part, on ne manque pas de constater des faits troublants et peu favorables à la conception que nous venons de rappeler. Ce sont ces faits que nous voudrions brièvement exposer ici.

Voyons d'abord dans quelles circonstances et dans quelles régions s'observe la métaplasie malpighienne des muqueuses cylindriques. Pour répondre à cette question, il ne faut envisager que les cas où la métaplasie apparaît réellement démontrée. Or, il est évident que la présence d'un ilot malpighien parfaitement circonscrit au milieu d'une muqueuse cylindrique n'est pas une preuve d'un processus métaplasique, il peut tout aussi bien s'agir d'une malformation embryonnaire. Nous admettons par contre l'existence d'un processus métaplasique lorsque l'apparition du tissu malpighien s'observe avec une certaine fréquence dans des conditions étiologiques identiques et surtout lorsque la présence de formes intermédiaires permet en quelque sorte de suivre l'évolution du changement structural. Encore faut-il que, dans tous ces cas, l'on puisse exclure, pour des raisons topographiques, l'immigration d'un épithélium malpighien de voisinage.

Ces phénomènes métaplasiques, indiscutables à notre avis, s'observent avec une grande fréquence dans tout le domaine des voies respiratoires. La transformation malpighienne du revêtement bronchique apparaît avec une

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rapidité parfois surprenante dans les processus inflammatoires subaigus et chroniques même chez l'enfant. L'épithélium bronchique, pourrait-on dire, a une tendance manifeste à devenir malpighien.

Au niveau du corps thyroïde la métaplasie malpighienne du revêtement acineux est plus rare, mais des recherches attentives permettent néanmoins de constater ce processus dans bien des thyroïdites chroniques. On observe alors la stratification de l'épithélium, la formation de bourgeons saillants à l'intérieur des vésicules dont les éléments cellulaires, de forme polygonale, sont, reliés entre eux par des filaments d'union.

Dans le domaine du tube digestif, la métaplasie malpighienne est presque propre aux glandes salivaires et au pancréas. En ce qui concerne les glandes salivaires, le fait est classique; il suffit de pratiquer la ligature du canal

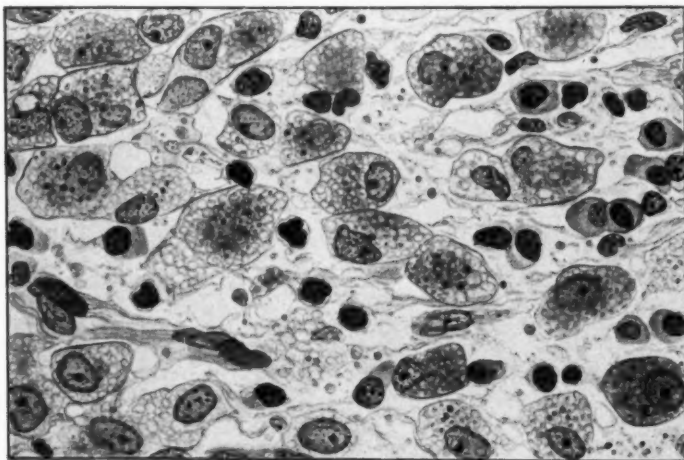


FIG. 1.—Îlot gastrique de l'œsophage au voisinage d'un épithélioma du type gastrique (à gauche).

excréteur ou d'injecter dans le système canaliculaire une substance irritante (goudron, huile de scharlach, etc. . . .) pour provoquer, à coup sûr, une transformation malpighienne de l'épithélium canaliculaire.

Dans le pancréas, l'un de nous a démontré que l'apparition de bourgeons malpighiens dans les canaux excréteurs est très fréquente dans les pancréatites chroniques.

Parmi les autres muqueuses, qui sont plus fréquemment le siège de métaplasies malpighiennes, il faut encore citer l'épididyme. Des recherches systématiques montrent que l'épithélium cylindrique de cet organe prend assez souvent des caractères malpighiens aussi bien dans les épидидymites subaigues gonococciques que dans les épидидymites tuberculeuses.

Au niveau du corps utérin, la fréquence de la métaplasie malpighienne, en dehors des tumeurs, a été l'objet de nombreuses discussions, mais nous considérons avec Kaufmann et beaucoup d'autres auteurs que ce fait est très rare.

Mentionnons encore que dans la glande mammaire la métaplasie malpighienne des conduits galactophores a été observée à différentes reprises et

provoquée expérimentalement par injection d'huile de scharlach (Fischer).

Quelles sont maintenant les conclusions que l'on peut tirer de ces faits d'observation?

En ce qui concerne le mécanisme même de la métaplasie épithéliale, le fait est aujourd'hui reconnu par tout le monde qu'il n'y a pas transformation structurale de cellules adultes; ce sont les cellules jeunes en voie de prolifération qui, en se différenciant, changent d'orientation et prennent un caractère différent de leur cellule-mère; la métaplasie est, suivant la formule de Lubarsch, une *régénération atypique*.

D'autre part, nous avons vu que la métaplasie malpighienne ne s'observe que dans des régions déterminées et ce fait montre nettement, à notre avis, que l'irritation chronique ne résume pas toute la pathogénie du processus. Si

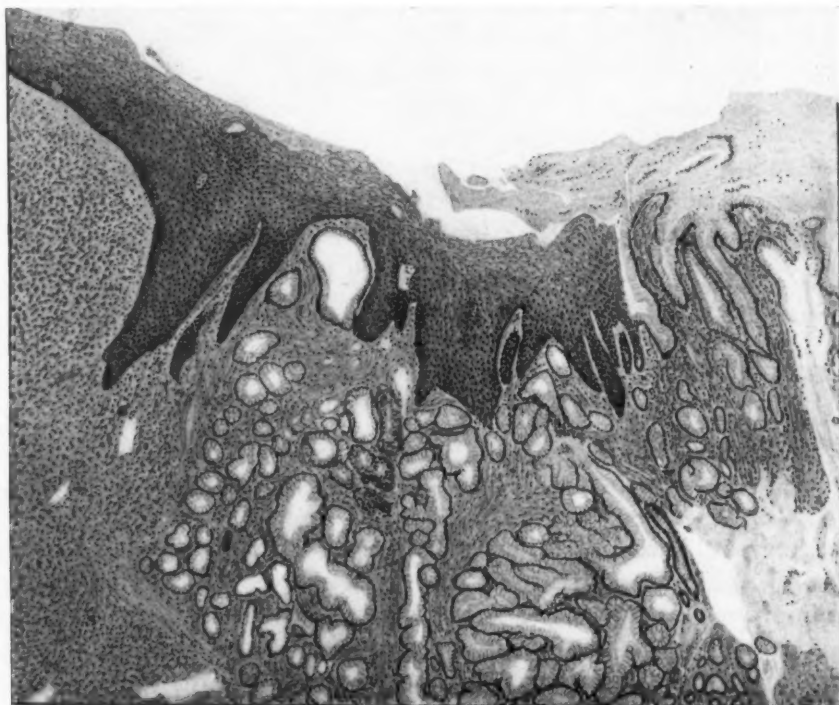


FIG. 2.—Aspect de la tumeur à un fort grossissement. On voit des cellules isolées remplies de mucus.

réellement la métaplasie était la conséquence directe d'un facteur irritatif exogène, non spécifique, elle devrait se réaliser beaucoup plus souvent et dans n'importe quel endroit. Or, on connaît des muqueuses telles que celle de l'estomac ou de l'appendice où les processus inflammatoires chroniques sont d'une extrême fréquence et où la métaplasie malpighienne n'a jamais été observée au moins chez l'homme. L'influence d'un facteur local semble donc indéniable et ce rôle du "terrain" que nous retrouvons avec toute son importance dans la pathogénie du cancer s'affirme encore davantage lorsqu'on étudie de plus près l'évolution du processus métaplasique.

On se rend alors compte que dans le domaine d'une muqueuse irritée où

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les mêmes conditions semblent réalisées sur une large étendue, la métaplasie n'est pas d'emblée diffuse—les éléments malpighiens apparaissent par îlots et ce n'est que plus tard que ces îlots s'étendent, gagnent la muqueuse environnante et arrivent finalement à la confluence. L'analogie de ce processus avec l'éclosion du cancer après goudronnage est frappante.

En invoquant donc l'irritation chronique comme facteur étiologique de la métaplasie, on n'explique rien. Tout indique l'intervention de facteurs très spéciaux qui ne se réalisent que dans des conditions déterminées; et ces facteurs, il faut l'avouer, nous les ignorons totalement.

Les mêmes difficultés se présentent, lorsqu'on cherche à préciser les rapports entre la métaplasie et les tumeurs hétérotopiques.

Pour les adeptes de la théorie irritative, les faits sont très simples: l'irritation crée la métaplasie et la métaplasie fournit le terrain sur lequel se développe la tumeur. La métaplasie prend ainsi la signification d'une *lésion précancéreuse*. Il faudrait alors s'attendre à trouver de préférence les épithéliomas hétérotopiques là où la métaplasie elle-même est fréquente.

En réalité il n'en est pas toujours ainsi.

Les épithéliomas malpighiens des *bronches* ne sont pas rares mais ils sont peut-être moins nombreux que la fréquence de la métaplasie ne le fait supposer. Si l'on considère, d'un côté, le nombre considérable des malades atteints de pneumopathies chroniques avec métaplasie malpighienne des bronches et qui restent indemnes de cancer, de l'autre côté, le nombre surprenant de malades atteints de cancer bronchique et qui n'ont jamais manifesté une atteinte inflammatoire antérieure broncho-pulmonaire, la métaplasie pavimenteuse des bronches cesse de figurer parmi les lésions précancéreuses (R. Huguenin).

Pour le *corps thyroïde*, les faits sont encore plus nets; alors que la métaplasie malpighienne y est relativement fréquente, les cancers malpighiens sont d'une grande rareté. Nous en avons trouvé une quinzaine de cas seulement dans la littérature (Kocher, Ribbert, Demme, Schmidtman, Eppinger, Lucke, Herrenschmidt, Masson, Reinstaller). Encore n'est-il nullement prouvé que tous ces cas relèvent réellement d'un processus métaplasique car le corps thyroïde est indiscutablement un siège d'inclusions malpighiennes congénitales (kystes dermoïdes dérivés du canal thyroéoglosse des fentes bronchiales, etc. . . .) qui peuvent tout aussi bien être le point de départ d'épithéliomas hétérotopiques.

La vésicule biliaire est sans conteste un des sièges de prédilection des épithéliomas malpighiens hétérotopiques (environ cinquante cas ont été publiés, dont deux personnels). Or, précisément dans la vésicule biliaire les processus métaplasiques sont d'une extrême rareté. Malgré des recherches nombreuses la métaplasie malpighienne n'y a été observée qu'une seule fois, par Lubarsch. Dans le *pancréas*, par contre, où les processus métaplasiques sont fréquents, les épithéliomas malpighiens sont beaucoup plus rares, sept cas seulement se trouvent signalés dans la littérature (Israël, Levisohn, Kawamura, Papadopoulos, Herxheimer, Oberling, Plenge); d'autre part, on a

observé dans le tube digestif des épithéliomas malpighiens dans des régions où l'on n'a jamais constaté de métaplasie, par exemple dans *l'estomac* (Eppinger, Rolleston, Rösig, Calderara, Lubarsch, Pollack, Herxheimer, Borst, Borrmann, Oberling et Wolf, de Martel, Oberling et Pernet) et dans le colon (Schmidtman, Herxheimer, Probst, Plenge).

Dans *l'épididyme*, où les processus métaplasiques sont très fréquents, les cancers sont très rares en général et les épithéliomas malpighiens sont exceptionnels; nous n'avons eu connaissance que d'un seul cas publié par Rowland Nicholson.

L'utérus par contre, très rarement atteint de métaplasie est fréquemment le siège d'épithéliomas malpighiens. Cette simple énumération montre qu'il

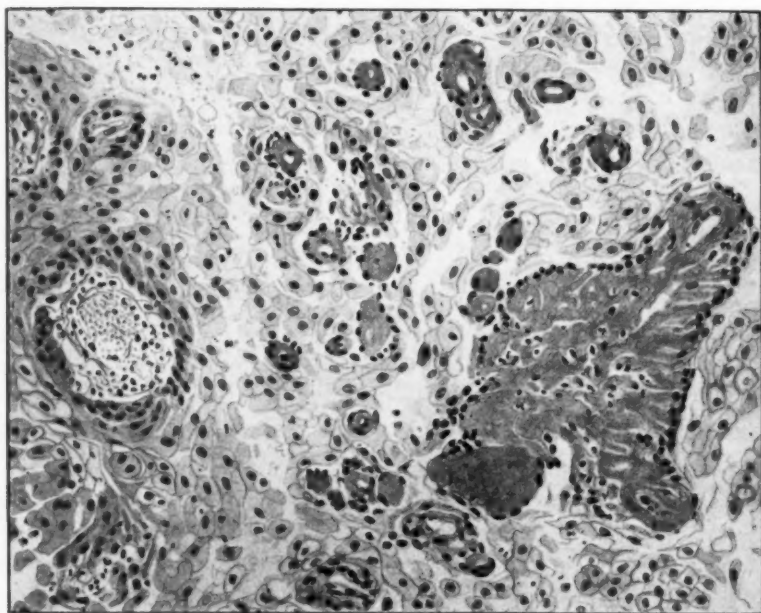


FIG. 3.—Épithélioma pavimenteux des plexus choroïdes. Papilles tapissées par des cellules polygonales de type malpighien.

n'y a aucune coïncidence entre la fréquence de la métaplasie malpighienne et la fréquence des tumeurs malpighiennes hétérotopiques.

Cette constatation qui paraît surprenante au premier coup d'œil s'explique lorsque l'on étudie de plus près la structure des tumeurs hétérotopiques.

Beaucoup d'entre elles en effet, montrent une structure mixte, à la fois malpighienne et cylindrique. Ce sont ces épithéliomas que les auteurs allemands désignent sous tel nom "d'adénocancroïdes."

Nous avons eu l'occasion d'observer récemment trois de ces tumeurs situées dans le corps utérin et qui peuvent servir d'exemple pour l'étude histologique de ces néoplasmes.

Dans le premier cas, il s'agissait d'une tumeur assez volumineuse, à surface bourgeonnante, occupant la partie supérieure du canal cervical, remplissant la cavité utérine.

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A l'examen histologique, on est frappé de voir dans cette tumeur deux structures absolument différentes. Dans sa partie inférieure le néoplasme offre l'aspect d'un épithélioma baso-cellulaire du col utérin, dans sa partie supérieure, celui d'un épithélioma cylindrique. Aux deux extrémités, ces deux structures sont absolument pures; ce n'est que dans la partie centrale du néoplasme où l'on assiste à une intrication des parties pavimenteuses et cylindriques.

Les deux autres cas sont des tumeurs qui, du point de vue macroscopique, réalisent l'aspect habituel du cancer du corps utérin: L'aspect histologique, identique dans les deux cas est très particulier. C'est l'image d'un épithélioma cylindrique parsemé d'innombrables îlots malpighiens; ces îlots sont absolument indépendants les uns des autres, ils se forment aux dépens de l'épithélium cylindrique qui change de forme, donne naissance à un amas de cellules qui fait saillie à l'intérieur du tube. Certaines de ces masses sont formées par des cellules polygonales qui ne présentent aucun attribut spécifique des cellules malpighiennes; dans d'autres, par contre, on voit apparaître des filaments d'union et des gouttelettes de kératohyaline. On voit même des cellules qui s'imbriquent, se disposent en couches concentriques autour d'une gouttelette de kératohyaline et esquissent ainsi la formation d'un globe corné.

Cette répartition différente des zones pavimenteuses et cylindriques que nous avons trouvé dans ces épithéliomas du corps utérin se rencontre également dans les épithéliomas de la vésicule biliaire, de l'estomac, du colon, bref, partout où des tumeurs hétérotopiques ont été signalées.

Ainsi ces épithéliomas à structure mixte peuvent réaliser deux aspects différents: tantôt les parties cylindriques et pavimenteuses sont nettement distinctes, tantôt la structure pavimenteuse apparaît un peu partout dans le domaine d'une tumeur dont la structure fondamentale est cylindrique glandulaire.

L'interprétation sera différente dans les deux cas. Dans la première éventualité, certains auteurs admettent l'existence de deux tumeurs différentes avec intrication secondaire. Le fait serait alors à rapprocher des cas où il y a manifestement association, en une même région, de deux tumeurs différentes comme par exemple d'un épithélioma et d'un sarcome; soit qu'il s'agisse de l'effet du hasard, soit que l'une de ces tumeurs ait déclenché la formation de l'autre. En ce qui concerne notre observation, on peut également penser que la cancérisation a intéressé la muqueuse préalablement métaplasiée et la muqueuse cylindrique située au voisinage.

Dans le deuxième cas il paraît évident que *la métaplasie s'est établie dans la tumeur en évolution*. Cette constatation est très importante car, étant donné le fait que les épithéliomas hétérotopiques se développent fréquemment dans des régions où la métaplasie est rare ou inconnue, il est permis de penser que, dans bien des cas, *la métaplasie ne précède pas le cancer mais qu'elle en est une conséquence*.

Ainsi, l'étude minutieuse des épithéliomas hétérotopiques n'est guère favorable à la thèse suivant laquelle la métaplasie doit être considérée comme une lésion précancéreuse.

Un autre fait vient encore restreindre l'influence de la métaplasie: dans la genèse de certains épithéliomas hétérotopiques: c'est le rôle des malformations embryonnaires.

Certaines hétérotopies congénitales peuvent occasionnellement devenir le point de départ de tumeurs malignes.

Nous figurons ici, à titre d'exemple, un épithélioma qui s'est développé dans le tiers supérieur de l'œsophage chez un homme adulte. Cette tumeur reproduit la structure caractéristique d'un épithélioma gastrique du type de la limite plastique. On voit dans un stroma très développé des cellules isolées; assez volumineuses, arrondies ou ovoïdes, remplies de gouttelettes de mucus. Dans le domaine de cette tumeur, la muqueuse œsophagienne se trouve interrompue par un îlot gastrique, reproduction fidèle de la muqueuse pylorique.

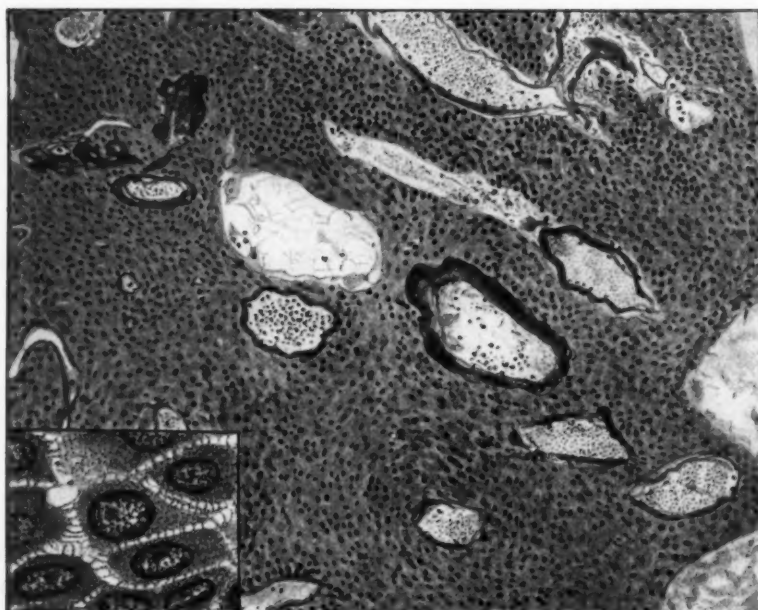


FIG. 4.—La même tumeur, région compacte.

Il paraît donc infiniment probable que cette tumeur a pris naissance aux dépens d'un îlot gastrique semblable, et personne ne songerait ici à soulever l'hypothèse d'une métaplasie.

Or, cette même interprétation s'impose lorsqu'une tumeur malpighienne se développe dans une région où la métaplasie est inconnue, et où l'existence de malformations embryonnaires est démontrée.

Tel est le cas des épithéliomas pavimenteux des plexus choroïdes.

C'est dans le travail de Boudet et Clunet que, pour la première fois, l'attention a été attirée sur ces tumeurs. Ces auteurs décrivent une tumeur papillaire, développée à la base du crâne, et adhérente au cerveau au niveau de la fente de Bichat. L'examen histologique montre de nombreux axes conjonctivo-vasculaires tapissés par un épithélium malpighien à évolution cornée incomplète qui présente des altérations secondaires multiples et variées.

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Boudet et Clunet donnent un aperçu bibliographique très complet d'où il ressort que des tumeurs malpighiennes ont été observées à différentes reprises dans le domaine de l'encéphale—notamment à la base du crâne, dans le troisième et dans le quatrième ventricule.

Un autre cas d'épithélioma malpighien du troisième ventricule a été décrit par I. Bertrand en 1924, et nous avons l'occasion d'y ajouter une nouvelle observation concernant un homme de vingt-six ans.

Au microscope, la tumeur montre une structure papillaire; on voit des axes conjonctivo-vasculaires tantôt grêles et délicats, tantôt épais et scléreux, tapissés par un revêtement malpighien caractéristique. Celui-ci présente des aspects un peu différents suivant les points. Dans certaines régions les cellules ont tendance à s'écarter, seules les cellules de la couche basale, qui se trouvent au contact du tissu conjonctivo-vasculaire, restent serrées les unes contre les autres; elles se distinguent des autres par leur taille réduite—ce sont des éléments cylindro-cubiques—et par la basophilie de leur cytoplasme.

Dans d'autres régions, le tissu néoplasique est plus dense, les cellules se tassent les unes contre les autres, forment des plages plus ou moins étendues, interrompues seulement par des axes conjonctivo-vasculaires. Les cellules, à ce niveau, montrent l'aspect caractéristique des cellules malpighiennes: elles sont réunies entre elles par des filaments d'union et, ça et là, on remarque des boules de kératohyaline.

A l'autopsie, la base du cerveau paraît nettement bombée dans la région de l'infundibulum. En pratiquant des coupes frontales, on se rend compte que le troisième ventricule est rempli d'une masse tumorale anfractueuse de la grosseur d'une noix. La tumeur a fortement distendu les parois ventriculaires, les couches optiques sont écartées mais le tissu cérébral environnant n'est nullement infiltré. Les deux ventricules latéraux sont considérablement distendus mais indemnes de néoplasme.

Peut-on incriminer dans la genèse de ces néoplasmes un processus métaplasique? Nous ne le croyons pas, et pour les raisons suivantes:

(1) La métaplasie, dans le domaine de l'encéphale (plexus choroïdes, épendyme), n'a jamais été observée.

(2) Ces tumeurs se développent sans exception, au voisinage de la base du crâne, (troisième ventricule de préférence), dans une région où l'existence d'hétérotopies malpighiennes a été démontrée à de multiples reprises.

(3) Ces tumeurs s'observent souvent chez des sujets jeunes (Cas Mott et Barrat, trente-quatre et vingt-huit ans, cas Saxer quarante-six ans, cas Bergmann et Steinshaus sept ans, cas Mackay et Bruce seize ans, cas Boudet et Clunet huit mois, cas Bertrand cinquante ans, cas personnel vingt-six ans).

Il semble donc logique d'admettre que ces tumeurs ont eu pour origine une hétérotopie congénitale, mais ce fait n'implique à notre avis aucune interprétation pathogénique. La malformation embryonnaire n'explique pas la *genèse*, mais uniquement la *structure hétérotopique* de la tumeur—elle n'est pas une lésion précancéreuse, pas plus que la métaplasie. La preuve réside précisément dans ce fait que certaines malformations telles que les

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îlots gastriques de l'œsophage sont extrêmement fréquentes alors que leur transformation cancéreuse est très rare. Cela prouve que dans l'interprétation histogénétique des tumeurs hétérotopiques un certain éclectisme est nécessaire.

CONCLUSIONS

Certaines muqueuses cylindriques sont fréquemment le siège d'une métaplasie malpighienne, mais dans aucune de ces régions le pourcentage des tumeurs malpighiennes ne devient prédominant; dans plusieurs de ces régions même, les épithéliomas malpighiens sont remarquablement rares. On ne peut donc pas considérer la métaplasie comme une lésion précancéreuse.

Bien souvent par contre, la métaplasie ne s'extériorise que dans une tumeur en évolution; elle est alors consécutive à la cancérisation. Ce fait s'observe notamment dans certains organes tels que la vésicule biliaire et l'utérus où la métaplasie malpighienne, en dehors des tumeurs, est extrêmement rare.

Il en résulte que, du point de vue pratique, l'interprétation de la métaplasie épithéliale doit varier suivant les organes. Dans les bronches, dans le pancréas, dans l'épididyme, la métaplasie n'est nullement l'indice d'une cancérisation imminente, tandis que dans l'utérus, la présence d'îlots malpighiens est souvent le signe d'une cancérisation déjà établie.

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TREATMENT OF MALIGNANCY

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NO ONE can write adequately of any phase of the problems presented by malignant disease without acknowledging his debt to James Ewing. While the surgeon is primarily concerned with the possibilities of the removal of an invaded tissue, in the matter of the extent of operation in each case he must be guided by his decision as to whether the growth is truly benign, premalignant or frankly malignant. Doctor Ewing's purpose, as expressed in his preface, is to contribute something toward the reduction of mortality from cancer. Since it is only by increasing knowledge of the nature of cancer that mortality from this disease can be reduced, he has certainly made a great contribution toward the attainment of this purpose. Ever since the appearance of the first edition of "Neoplastic Diseases" in 1919, my associates and I have constantly made use of the wealth of information contained in that and in the succeeding editions.

While neither the cause of malignant disease nor its cure has yet been found, despite world-wide researches and vastly extending clinical experience, nevertheless great progress toward the conquering of this scourge of the human race has been made by the disproof of many false theories, by the discrediting of many so-called "cures," the studies of the incidence of malignancy in relation to age, race, climate, and the different bodily tissues, by investigations of its method of growth, and by the observation of the effects upon it of various physical and chemical agents. From all of these studies the practical results have been meager. We have learned, however, that cancer, whether of the external and visible parts or of the internal, invisible organs, obeys one general law of growth, and the old dictum based entirely upon clinical experience is established more uniformly than ever—namely, that the one and only cure for cancer is its early and complete removal. It is probable that with extending knowledge of the operation of physical laws in biological processes, new light may be thrown upon the causation of malignant growths, and that from this knowledge new methods of cure may be evolved. Already, investigations have shown that the electric capacity and conductivity of cancer of any part far exceeds the capacity and conductivity of the normal tissue, while the potential in cancer is opposite to that in normal tissue. The histologic appearance of a cancer offers a static picture of the cells. The capacity and potential measurements present the dynamic status of the cells, and it is with the dynamic status of the cells that we are primarily concerned in interpreting the status of any malignant or pre-malignant condition.

Whatever these and other researches may disclose to us in the future, at present the one sure method of approach to the cancer problem is that

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based upon clinical experience. I propose, therefore, to offer in this paper a review of the methods employed by my associates and myself in dealing with cancer of the various tissues, these methods being based upon our experience in 7,390 cases of malignancy.

It is of interest to note, in regard to cancer of the external parts, that, to my knowledge, no case of cancer has been observed on the normal, uninjured skin. The skin of the face, in particular, offers an opportunity for the study of the natural development of cancer which is of greater value than that of any condition induced in the laboratory. I have never seen a cancer develop upon the healthy skin of the face. It is always preceded by a pre-cancerous stage, a keratosis, a mole or wart, a benign tumor or ulcer. The pre-cancerous history is often a long one—of little scales picked off as frequently as they recurred, of a wart goaded by constant picking. In the case of a cancer on the buccal surfaces also there is usually a history of trauma from a rough tooth, from leucoplakia, or a fissure.

If in the cancer period of life every unhealthy scar were excised and the surface covered by skin grafting, if every chronic irritation were removed, if every ulcer were healed soundly, or excised and the surface covered by skin grafting, if every wart and mole were excised, if the mouth were kept wholesome, the teeth smooth and even, it would be found that the problem presented by cancer of the outer surfaces of the body would be well-nigh solved.

Since cancers obey one general law of growth, we may be sure that cancers of the inner, hidden parts follow the same course as do cancers of the skin. We must conclude, therefore, that internal cancers have their pre-cancer stages—chronic irritation, ulcerative benign growths, etc. Thus in the larynx the pre-cancerous state may be a syphilitic ulcer or a papilloma; in the stomach it may be a chronic ulcer; in the gall-bladder, irritating gall-stones and chronic inflammation; in the large intestine and rectum, ulcers and irritation from various sources; in the breast, chronic inflammation, benign tumors of certain types and senile changes; in the uterus, the irritations of pregnancy and senile changes, and benign growths; in the kidney and bladder, stones and benign growths.

Unfortunately, not all pre-cancerous conditions of the internal organs are amenable to treatment, but to the extent that these pre-cancerous states may be corrected, to that extent will the problem presented by cancer of these parts be solved.

Once the pre-cancer stage has passed, then complete removal of the growth—whether by excision, or by the X-ray or radium—becomes the only safe procedure. It is interesting and encouraging to note that increasing numbers of patients consult the surgeon as soon as any symptoms are presented which indicate an abnormal condition of any organ or tissue; in consequence, the percentage of cases of cancer which are caught in their early stages is increasing. Unfortunately, however, some of these internal cancers are symptomless in their earliest stages, so that when they come to operation

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they are so far advanced that even if removal of the local growth is still possible, there is danger that distant metastases are present.

It remains to discuss the treatment most preferred by my associates and myself for cancer of the various organs and tissues.

The Skin.—In our experience in the treatment of 629 cases of carcinoma of the skin and subcutaneous tissues, we have found that radium is the most efficient treatment, except in the case of a pigmented mole, which should always be excised.

The Jaws and Buccal Surfaces.—Our records include 549 cases of carcinoma of the buccal surfaces and jaw. Among these, 21.3 per cent. were cases of carcinoma of the tongue, 43.3 per cent. were carcinomata of the lip, and 13.3 per cent. were carcinoma of the jaw. Among the cases on which we have follow-up data, 25.37 per cent. have lived for five years or more.

Some years ago a study of 4,500 reported cases of cancer of the head and neck was made for me by Dr. F. W. Hitchings, who found that in less than 1 per cent. of these cases secondary cancer foci were found in distant organs and tissues. In cases of cancer of the head and neck, therefore, death, when it occurs, is almost invariably the result of the local development of the disease, the reason for this localization being the extraordinary barrier formed by the collar of lymphatics in the neck, every portion of which is readily accessible to the surgeon. Above this lymphatic collar, however, metastases are rapidly disseminated. In contradistinction to cancer of the skin and superficial parts which metastasize late, and are effectively treated by the local application of radium and the X-ray, cancer of the buccal surfaces demands the complete removal of the glands of the neck on both sides. In early cases of cancer of the jaws, on the other hand, since this condition metastasizes slowly, and usually only on the side of the lesion, a less radical operation is indicated, but in the advanced cases of cancer of the jaws, a wide regional block dissection is indicated.

As for the removal of the primary focus, an early cancer of the lip is usually successfully treated by radium; early cancer of the tongue or of the buccal cavity may be treated by radiation, or perhaps better by electro-coagulation. Every case of advanced cancer of the lip or tongue should be excised, and as stated above, the lymphatic glands of the neck should also be removed by wide block dissection. In cases of carcinoma of the jaws a "platter" of underlying bone should be removed together with the intact growth.

It should be emphasized that while radiation of the local lesion may be indicated, radiation of the involved lymphatic glands of the neck should never be done, as this treatment cannot be depended upon. If the glands of the neck have been irradiated and the patient has recovered, we must conclude that the glands of the neck probably were not involved. After operation on any part of this field, post-operative treatment with deep, accurately measured X-ray or radium radiation is of advantage. Always in these cases

should be borne in mind the prime importance of the minimum handling of the carcinomatous tissue and the avoidance of the implantation of cancer cells in the operative field.

The Larynx.—Our series includes 134 cases of carcinoma of the larynx, in fifty-seven of which operation was performed. Among those patients on whom we have follow-up data, 63.2 per cent. have survived for more than five years.

Cancer of the larynx calls for laryngectomy, which is one of the most successful operations for the permanent cure of cancer. Here, as nowhere else in the body, except in visible parts, the presence of cancer is evident in its earliest stages, for it is announced by every spoken word of the patient. Moreover, in cases of intrinsic cancer of the larynx there is practically no lymphatic involvement, for the reason that intrinsic cancer of the larynx is, as it were, confined in a box through whose walls the cancer cannot penetrate, for cancer cannot penetrate through hyaline cartilage. There is no other situation in the body in which cancer declares itself immediately and from which it cannot be disseminated into the lymphatic glands. If a cancer of the larynx is extrinsic, then because of the abundance of lymphatic connections, it will extend rapidly, and generally operation is, at best, only a palliative remedy. In such cases the only hope lies in the local removal of the growth and block dissection of the gland-bearing area. In operable cases in which only tracheotomy can be attempted, radium is of value as a palliative measure.

For intrinsic cancer of the larynx, as stated above, laryngectomy is indicated, the general trend of opinion being against the use of radium, for laryngectomy offers a practical certainty of cure, provided the cancer is entirely intrinsic. The post-operative application of the X-ray, however, may be of value, as it may check any extension of the growth provided some undiscovered extrinsic focus exists, or provided some cancer cells have become implanted.

The Thyroid Gland.—In our total series of thyroidectomies, there has been a carcinoma of the thyroid gland in 268 cases. In about 90 per cent. of these cases the carcinoma was due to the degeneration of an adenoma. For this reason I believe that all adenomata should be removed. Thus the treatment of carcinoma of the thyroid gland, like the treatment of goitre, is mainly a problem of prevention. If the case is operable, there is no question as to the treatment; the only difficulties are presented by the inoperable cases in which the patient is suffering from obstruction and partial asphyxiation. In such a case the implantation of radium is indicated, together with a decompression operation if the distress of the patient demands immediate relief. In this operation the preglandular muscles are divided, thus relieving the back pressure of the gland upon the trachea.

Sometimes as the result of radiation the carcinoma will disappear; in other cases radiation seems to be of no avail. Radiation may produce myxoedema, but this is readily overcome by the administration of thyroid

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extract. What the end-result of decompression and radiation may be in any given case cannot be foretold, but the patient is certain to have a period of relief. It must be borne in mind that involvement of the neighboring tissues is almost sure to be present, and that if the cancer involves the trachea there is practically no hope of cure.

The Œsophagus.—Our total series includes 111 cases of cancer of the œsophagus, in the majority of which the symptoms had been present for less than six months. This is one of the most hopeless of malignant conditions, for when the patient presents himself it is usually too late for surgical treatment to be of any value. The emaciation and weakness due to the dysphagia, which is the prominent symptom, in itself makes every case a poor surgical risk. In most of our cases dysphagia was already so marked as to have produced extreme emaciation and exhaustion.

None of the cases of cancer of the œsophagus in our series have survived for more than thirty-four months.

The Breast.—Our total series includes 1,350 cases of cancer of the breast, fourteen in males. In 789 cases the patients have been treated by surgery alone; in 398 by surgery and radiation. Of the patients regarding whom we have follow-up data, 25.70 per cent. have survived for five years or more.

According to Ewing, the United States Census for 1914 reported 5,423 deaths from cancer of the breast among 52,420 total cancer deaths, an incidence of over 10 per cent.¹ I am inclined to believe that the 1930 census will present a lower incidence, since, as the result of increasing knowledge on the part of the laity of the symptoms of the early stages of cancer, especially of cancer of the breast, the number of patients who present themselves with inoperable cancer of the breast is constantly diminishing. The majority of women are now ready to consult their physician upon the first appearance of any abnormality in the breast.

The problem for the surgeon, therefore, has become one of accurate differentiation between benign and malignant tumors. Frank cancer is easily diagnosed, but the diagnosis of border-line cases is by no means a simple problem. Bloodgood at one time submitted specimens from over sixty border-line cases to a number of pathologists. These pathologists were divided into two groups, one of which favored a diagnosis of cancer, the other believed the growth to be a benign lesion. "In not a single case has there been a uniform agreement as to whether the lesion was benign or malignant."²

Ewing states that "the great majority of mammary cancers are rather easily recognizable by inspection and palpation."³ In cases in which the clinical symptoms and the frozen section cannot give absolute proof of the character of the tumor, the utmost safety of the patient demands the complete excision of the breast and of the regional lymphatics, for unlike cancer of the head and neck or the imprisoned, intrinsic cancer of the larynx, the abundant, lymphatic channels from the breast may readily and easily produce thoracic and abdominal metastases.

Among the so-called benign breast lesions which are possibly precancerous are diffuse hypertrophy, traumata, chronic mastitis, and cysts, as well as the so-called benign tumors.

In regard to the so-called benign tumors, Deaver has stated, "Tumors of certain types having certain structure are constantly harmless; those of other types, having another structure, are persistently invasive, destructive and constantly fatal. Unfortunately these are the extremes of a series between which lie many tumors that may or may not be harmful, or whose structures may fail to give a clue to their true disposition."⁴ I am far from recommending the radical operation in every case of tumor of the breast, but I do wish to emphasize the importance of frequent examination of the breast after the local excision of what appears to be a benign tumor, so that the radical operation may be performed immediately if the lesion shows any suspicion of malignancy. A biopsy should never be performed, for if the growth should prove to be malignant there is danger of its dissemination, and whatever its character, in any case it should be removed entirely and then sectioned.

As for the rôle of radiation—from a study of the end-results in our series, Portmann draws the following conclusions:⁵

"1. Intensive X-ray therapy, especially by the cross-fire method, is not the preferred procedure or the post-operative treatment of carcinoma of the breast.

"2. Post-operative X-ray therapy by moderate repeated dosage decreases the number of recurrences and metastases, and prolongs the life of many patients suffering from carcinoma of the breast."

We, therefore, give radiation therapy as soon as possible after operation, not waiting until the wound is healed. Only if a case is entirely inoperable is radiation employed as a palliative measure instead of surgery.

The Stomach.—A study of the records of our 648 cases of cancer of the stomach shows that the history is commonly a history of indigestion or of ulcer; that ulcer of the stomach has a distinct potentiality as a precancerous condition; that the history and the X-ray findings are the most valuable means of diagnosis; that a differential diagnosis between an old ulcer and early cancer cannot be made with certainty; that when the probability of cancer is suspected an exploration should be made at once. In late cases, as in late cases of cancer elsewhere, even though the operation is survived and the local lesion removed, there is great danger of metastases, especially in the liver or retroperitoneal glands.

A cancer of the stomach is characterized by such a rapidity of growth and such an extent of lymphatic involvement that an inoperable stage is reached very early in its progress. Since the earliest stages are practically symptomless, and the earliest symptoms are those of more or less mild indigestion, in the majority of cases the patients come too late for possible cure.

The operation indicated is the widest possible excision of the growth,

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and the patient should be offered every safeguard and aid that surgery has to offer. By the use of blood transfusion, saline injections, diathermy during and after the operation, the application of hot packs, and a divided operation in many cases in which the prognosis appears to be hopeless, the patient may be carried through to cure or to a comparatively comfortable prolongation of life. In regard to the divided operation, it may be added that in certain cases in which the diagnosis of cancer has been made, the supposedly cancerous mass has disappeared in the interval between the two stages so that the second stage has not been required.

Among our cases of cancer of the stomach, of those patients on whom follow-up data are available, 4.44 per cent. have passed the five-year period. Resections have been made in ninety-five cases with five-year survivals in 6.94 per cent.; gastroenterostomy in 168, with five-year survivals in 5.21 per cent.; and radiation therapy alone in twenty with no five-year survivals. In the last two instances, perhaps our diagnosis may be questioned, but in each of these cases the clinical signs, the X-ray picture and the exploratory operation gave every evidence of an inoperable carcinoma.

Gall-bladder.—Our records include sixty-four cases of carcinoma of the gall-bladder and bile-ducts among which operations were performed in twelve cases. We have a record of two five-year survivals.

If a patient presents symptoms referable to the gall-bladder of more than one year's duration, the possibility of malignancy of the gall-bladder should be considered. Cancer of the gall-bladder is usually associated with cholecystitis, and consequently in many cases the patient is treated for the latter condition until the disease has extended into the liver and deep structures. Then when its malignant character is recognized, it is too late for operation to be of any avail. If the presence of the malignant condition is recognized before extension to the liver has occurred, then an immediate cholecystectomy is indicated.

The Liver.—Of cancer of the liver it is necessary to state only that it is rarely primary and is always incurable. Only palliative efforts can be made and their effect at best is but temporary. Our records include 103 cases of cancer of the liver, among which three were shown at autopsy to be primary.

The Intestines and Rectum.—Our total series of cases of carcinoma of the large intestine and rectum includes 685 cases. Of the cases in regard to which we have follow-up data, 8.45 per cent. have survived for five years or more.

The diagnosis of carcinoma of the small intestine is made from the history and clinical signs and the X-ray picture. If the presence of a cancer is indicated then an exploratory operation should be performed to determine operability, with immediate removal of the growth if possible. As in the case of carcinoma of the stomach, every available method for the conservation and restoration of the patient should be employed. Our records include twenty-one cases of carcinoma of the small intestine.

In cases of carcinoma of the large intestine and rectum, a colostomy should be performed, followed by radical operation, X-ray radiation being

employed after the operation. In cases in which the growth is so low in the rectum as to be readily accessible, the implantation of radium needles and the application of radium packs may be sufficient. In inoperable cases a colostomy should be done, followed by radiation. There should be a period of about ten days between the colostomy and the final operation, or rather, between the colostomy and the decision as to the method of treatment, as a period of that length is necessary to allow the inflammatory reactions of the disease to subside sufficiently to make it possible to determine what operation shall be performed. This decision depends, of course, upon the findings of an exploratory operation. The entire picture may change during this period.

While the application of deep X-ray radiation is beneficial after operation or after radium treatment, it is of little, if any, value in the treatment of recurrences.

A statistical study of cases treated at the Cleveland Clinic since 1921 shows the following survival percentages:

CANCER OF THE RECTUM AND SIGMOID

Treatment	Total cases	Traced cases	Survival more than five years
Resection.....	145	125	7.2 per cent.
Resection and radiation.....	39	34	20.6 per cent.
Colostomy only.....	108	63	0 per cent.
Colostomy and radiation.....	76	70	10 per cent.
Radiation only.....	36	27	7.4 per cent.

These figures show, as Jones⁶ has reported, that although operation by the abdomino-perineal route, combined with radiation, is the treatment of choice, if operation is refused or if the condition is inoperable, there is sufficient evidence that a cure can be obtained in certain cases and marked palliation in others by the use of radium and Röntgen-ray.

The Genito-urinary Organs.—The records of Doctor Lower and his associates at the Cleveland Clinic include 805 cases of malignant disease of the genito-urinary organs—335 of the bladder, 124 of the kidney, 16 of the urethra, two of the ureter, 268 of the prostate, and 60 of the testicle.

Among these cases in which the results are known, there have survived for five years or more 9.84 per cent. of the cases of malignant disease of the bladder, 8.74 per cent. of the cases of malignant disease of the kidneys, 3.75 per cent. of the cases of carcinoma of the prostate.

In general, malignant tumors of the genito-urinary organs are best treated by surgery with the addition of radiation in certain cases. In inoperable cases, radiation may be the only available method of treatment.

In some cases, tumors of the kidney in children may be reduced by deep X-ray therapy, but the radiation must be followed later by surgery.

For malignant tumors of the kidney in adults, the indicated treatment is surgery with radiation both before and after operation. In many cases radiation will so reduce the size of the tumor that cases which have seemed to be inoperable become operable. Tumors of the kidney should be irradiated

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no matter how hopeless the outlook. In the case of deep-seated bladder tumors, radium has seemed to prevail in certain cases, but the results are too uncertain for radiation to be used routinely. Post-operative radiation is employed in many cases, but principally because of the hope that it may be of avail rather than because of any definite results that have been secured up to the present time.

Malignant tumors of the testes are treated by surgery with radiation both before and after operation.

Whether or not prostatectomy or radiation is the preferred treatment for carcinoma of the prostate remains to be decided. We believe that prostatectomy is to be preferred in uncomplicated cases, but we know that in cases in which a high blood urea cannot be reduced, radiation may provide the only possible method of treatment, or it may tide the patient over until prostatectomy can be performed.

The Uterus.—Our records include 783 cases of carcinoma of the uterus. Of the 211 cases of carcinoma of the fundus, 14.84 per cent. of those patients on whose cases we have follow-up data have survived for five years or more.

Of the 572 cases of carcinoma of the cervix we have follow-up data in 208 cases treated by radiation, and in 129 cases treated by surgery, before we adopted our present policy—9.13 per cent. of the former and 17.05 per cent. of the latter have survived for five years or more.

The preferred treatment of carcinoma of the fundus still seems to be *sub judice*—both as to whether surgery or radiation is the treatment of choice, and as to the type of operation to be performed.

As to carcinoma of the cervix, on the other hand, the preëminent value of radiation appears to be established. At the Cleveland Clinic we now use radiation rather than surgery in the treatment of carcinoma of the cervix, reserving our final judgment until sufficient time has elapsed for a definite comparative study of the end-results.

As the presence of any but a frankly benign tumor of the breast demands the removal of that organ, especially in a patient past middle age, so when an intermittent or continuous uterine discharge occurs in a patient who has passed the menopause, we believe that a complete hysterectomy should be performed at once. Even if the character of the discharge does not appear to indicate the presence of a malignant condition, this operation should be performed without delay. In such cases curettage is contra-indicated, as, if cancer is present, the cancer cells will be disseminated.

In inoperable cases of carcinoma of the fundus, deep X-ray therapy is of value as a palliative agent and for the prolongation of life.

In the treatment of carcinoma of the cervix, both radium and deep X-ray therapy are used, the former being applied in needles and by radium packs.

Ovary.—We have seen 128 cases of carcinoma of the ovary. This growth is rarely primary, and in cases in which it is primary the removal

of both ovaries is indicated. If the peritoneum is extensively involved, deep X-ray therapy may retard the progress of the disease.

There have survived, for five years or more, 7.57 per cent. of our cases.

Bone.—Exclusive of carcinoma of the jaw, we have seen 161 cases of malignant disease of bone. It is still uncertain whether a primary malignancy of bone should be treated by X-ray or by surgery, but two things are certain: first, if an operation is performed, it should be preceded and followed by X-ray radiation, and second, if the condition is in a limb, amputation should immediately follow radiation, provided the condition is not inoperable. As for metastatic tumors, palliative treatment by the X-ray is the only therapeutic measure. Radium is contra-indicated as it would destroy the periosteum, and necrosis would follow.

The data which are being accumulated by the Registry of Bone Sarcoma of the American College of Surgeons may finally lead to a decision as to the relative merits of surgery and of radiation in the treatment of malignant diseases of bone.

Malignant tumors of other tissues might be included in this discussion, but in some instances they are exceedingly rare; in others they are practically never primary; in some they belong in the domain of the specialist. We shall only add here that in these cases the same rule applies as in those we have discussed above, that is, removal of the tumor by the most effective method if the site and extension of the tumor and the condition of the patient permit.

Finally, it may be emphasized that, whatever his present point of view regarding the method of choice in the treatment of a malignant tumor of any organ or tissue, the surgeon must hold himself in readiness to alter that view if accumulating experience indicates that other methods are to be preferred or are at least worthy of trial. It may be that as the result of the researches—clinical and experimental—which are in progress in many clinics and laboratories, some new and effective measure may be developed of which we should be ready to avail ourselves.

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EPIDERMOID CARCINOMA IN SEBACEOUS CYSTS

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FROM THE DEPARTMENT OF PATHOLOGY OF THE STEINER CANCER CLINIC

THE very common sebaceous cyst or "wen" is usually considered a very harmless lesion. However, it is certain that a number of these cysts eventually develop into malignant tumors. Statistics are of comparatively little value, for the vast majority of such cysts are not subjected to microscopical examination following their removal, and in a goodly number of cases, it is the development of a malignant tumor which calls attention to a lesion which may not have been previously observed, or in which little or no evidence of its development on or in a benign cyst can be detected.

Again, cysts may have been removed and there follows after a variable period of time, a recurrence in or near the scar, which recurrent tumor the surgeon is more apt to have examined than the primary cystic mass. That carcinoma does develop in a number of these cysts is well recognized by some writers, for one is able to find a number of references in the literature.

It seems reasonable to assume that a sebaceous cyst would be a fertile field for the development of malignancy when we consider certain factors which are present, and which are recognized as having considerable bearing on the development of carcinoma elsewhere. The formation of the cyst is due to mechanical blocking of the duct followed by retention of secretion. This is accompanied by a continued and increased activity of the cells within the cyst, for it may be that the cells become overactive as a result of the chronic irritation of retained secretion. To this add infection, either acute, chronic, or both, and we have a possible stimulus for the development of a malignant tumor.

Most of the patients with a sebaceous cyst usually give a history of its having been present for a considerable period of time before they seek its removal. Multiple cysts are quite common, and while a number of cases of carcinoma have occurred in patients with multiple cysts, yet multiple carcinomas in such cysts are unusual.

Broders and Wilson¹ reserve the name "sebaceous cyst" for those in which is found sebaceous material, white and granular with an offensive odor, while they designate the firm, solid tumors with lamellated structure as "keratoma." They believe that the latter arise from the lining cells of the duct and not from the gland proper. This would seemingly favor the development of squamous carcinoma, and yet we have been unable to find carcinoma in any "keratoma," all of our cases apparently arising in true sebaceous cysts, with perhaps one exception, one patient applying for treatment with a large recurrent tumor, and the history that "a sebaceous cyst had been removed some time before."

Ewing² mentions the development of carcinoma in sebaceous cysts, with a "structure recalling the cells of the ducts." Caylor³ reviewed the subject in

1925 and reported twelve cases from The Mayo Clinic. He also called attention to the fact that the actual percentage of malignant tumors is probably higher than it should be because many simple cysts were not sent to the laboratory. He found twelve malignant tumors in a series of 236 cysts, a percentage of 3.44.

In this laboratory 119 cysts and keratomas have been examined. Of this number, eleven showed definite carcinoma, and two others such marked epithelial activity as to be classed as "pre-cancerous." One case was diagnosed clinically as malignant at the time of admission.

Apparently the tendency toward malignancy, as in other forms, increases as the patient grows older, although a few cases have occurred in comparatively young individuals. In our series, the average age for all benign cysts was 38.3 years, the youngest patient six and the eldest seventy-six. In the



FIG. 1.—Epidermoid carcinoma in sebaceous cyst of scalp. Grade I, Case XI.

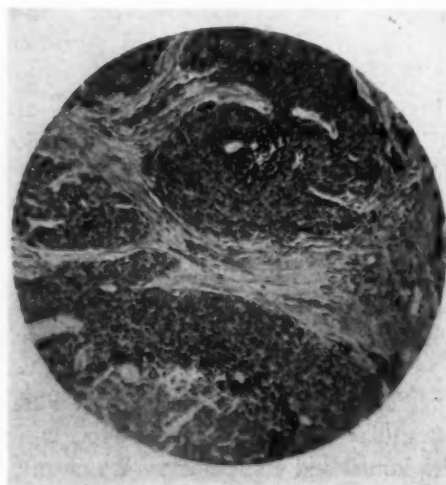


FIG. 2.—Epidermoid carcinoma in sebaceous cyst of scalp. Grade III, Case II.

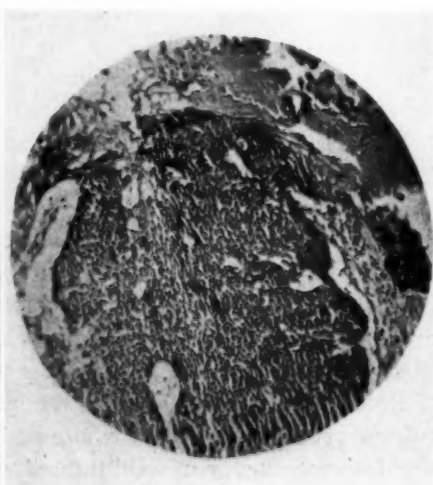


FIG. 3.—Epidermoid carcinoma in sebaceous cyst of arm. Basal cell. Case VIII.

eleven cases of carcinoma, the average age was 64.2 years, the youngest thirty-nine and the eldest eighty-three. All of these patients were over fifty except the one aged thirty-nine. The percentage of carcinoma in the whole series was 9.2. Ricker and Schwalb⁴ reported forty-three cases, of which

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thirty-nine were over forty years of age. In other reports there are recorded cases of malignancy in sebaceous cysts in patients, thirty-eight, twenty-seven and twenty years of age.

Patients with cysts were almost equally divided as to sex in our series, fifty-four female to fifty-two male.* However, the proportion of carcinoma in cysts in the female was much greater than in the male, a proportion of 8 to 3. It is interesting to note that there was only one case occurring in a negro, and that one a malignant cyst of the scalp.

The influence of direct trauma in the development of carcinoma in cysts of the scalp may be of some importance in a few of the cases. One of our series gave a history of scratching the cyst with a comb, while another stated that the cyst had been bruised against a table top. However, the other cases gave no definite history of any injury.

As to location, the scalp and face seem to be the more common locations for both simple and carcinomatous cysts. In Caylor's series³ all but two occurred above the shoulders, while Ricker and Schwalb⁴ found the face to be the most frequent location.

Most of the tumors reported by various writers have been of squamous type. A few cases of basal-cell carcinoma are reported, but none of these have occurred in the scalp. The case reported by Narat⁵ was a rodent ulcer in the skin *over* a cyst of the scalp but not *in* the cyst itself. Seff and Berkowitz⁶ reported two squamous-cell tumors of the scalp and temporal region, and a rodent ulcer of the forehead. Busfield's case⁷ was a rodent ulcer developing in a cyst of the forehead, which had been present for a number of years in a seventy-year-old patient, the tumor eventually involving the entire side of the face.

The structure of epidermoid carcinoma in sebaceous cysts varies to a moderate degree. For the most part, the cells are fairly well differentiated, with considerable hornification, pearls and spines. It is possible to find less differentiated areas in many of the tumors, but the proportion of adult structure is usually much greater. The grading of these tumors according to Broder's classification⁸ is of considerable value, for the more adult the tumor structure, the slower its growth and the less likely is it to metastasize beyond the nearest nodes. The few cases which have developed generalized metastases have been of undifferentiated types, Caylor's case being graded 4, and the fatal case of Seff and Berkowitz, from the pathological description, a grade 3. Gregersen⁹ reports a case with metastasis to the brain, grade unknown. The structure of the few basal-cell tumors has been quite characteristic of that group of tumors, and their course in keeping with such structure.

Recurrences following removal of these tumors are fairly common, especially if the skin is resected close to the tumor edge. In fact, the tumor itself

* The total number of cysts is greater than the total number of patients, for several patients had multiple cysts.

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TABLE I

Location of all cysts examined

Scalp.....	42	Chest wall.....	2
Face.....	16	Breast.....	2
Back.....	9	Finger.....	2
Ear.....	8	Hand.....	1
Forehead.....	8	Thigh.....	1
Cheek.....	7	Scrotum.....	2
Neck.....	3	Nose.....	2
Chin.....	3	Arm.....	1
Gluteal.....	3	Lumbar.....	1
Eyelid.....	2	Location unknown.....	2
Shoulder.....	2		

TABLE II

Epidermoid carcinoma in sebaceous cysts

No.	Sex	Color	Age	Location	Grade
1.....	M	W	50	Nose	Basal
2.....	F	W	83	Scalp	III
3.....	F	W	60	Scalp	I
4.....	F	W	72	Neck	I
5.....	F	W	60	Forehead	II
6.....	M	W	75	Face	I
7.....	F	W	65	Scalp	I
8.....	F	W	39	Arm	Basal
9.....	F	W	63	Cheek	III
10.....	M	W	76	Scalp	I
11.....	F	C	62	Scalp	I
<i>Pre-cancerous</i>					
1.....	F	W	60	Scalp	
2.....	F	W	52	Scalp	

may develop in a small fragment of a cyst incompletely removed. Metastases are comparatively infrequent, in spite of the three cases mentioned above. Our series fails to show any case in which metastases developed, although recurrences occurred in two.

Of the cases here reported, "pre-cancerous" case I died, some time after being seen in this clinic, of carcinoma of the breast with liver metastasis, which disease was present at the time of the removal of the cyst. Case II died three years after being seen, cause unknown. Case III died of pellagra about a year later. The remaining patients were without evidence of disease when last seen, although a few of them have been lost track of.

CANCER SERVICE IN MASSACHUSETTS*

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TO THE physician in general practice the cancer problem presents itself as perhaps the most difficult, the most distressing, and the most hopeless of all of the many baffling problems with which he has to deal in his daily rounds. The treatment and the care of many diseases is greatly aided by early recognition, but cancer is a unique disease in this respect, for while it is definitely and permanently curable in its early local condition, it rapidly extends beyond this favorable stage to become a fatal disease against which neither the natural defensive mechanism of the patient nor any known methods of treatment can do more than delay to a slight extent the inevitable fatality.

It is precisely for this reason that the diagnosis of cancer in its early stages is of such vital importance, and it is in its early stages that the diagnosis of cancer is most difficult. The diagnosis of advanced cancer is all too often unmistakable, but the early case of cancer may resemble any one of many different lesions which are not cancer. Indeed, the diagnosis of early cancer is frequently beyond the abilities of even the most experienced observer, and an exploratory operation, and a frozen section diagnosis by the pathologist, are necessary before a final decision can be made.

Such conditions amply justify the pessimism of the general practitioner in regard to the cure of cancer, and even the surgeon in the local hospital to whom he sends his patients tends to share this attitude. Most of the cases he sees are far too advanced to expect a cure by operation, and even in the occasional early case his previous experience leads him to have little faith in the possibility of cure, and he is tempted either to regard his work as palliative and to content himself with an operation of less extent than is considered necessary for the radical cure of the disease, or to refer the patient to the nearest X-ray operator, regardless of the apparatus or the experience in therapeutic X-ray that may be available.

We calculate that about 12,000 cases of cancer exist at any one time in Massachusetts, and we have over 6,000 physicians registered to practise in the state. This gives us an average of only two cases of cancer a year in the practice of each physician. When we consider the almost infinite variety of locations which cancer assumes it is easy to see that the general practitioner can never be expected to make himself or keep himself expert in the difficult task of the diagnosis of early cases, or to equip himself with the necessary resources for modern treatment.

* Remarks at the opening of a new building at the Pondville Hospital for the Treatment of Cancer of the Department of Public Health of the Commonwealth of Massachusetts, May 20, 1930.

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The physician in general practice, moreover, knows better than anyone else the mental and physical suffering, the distressing complications, and the long-continued and steadily progressing disability of the patient dying of cancer. And he is the first to appreciate the value of any such addition to his resources as is offered by the state in the Pondville Hospital. From the beginning of its service, three years ago, the Pondville Hospital has provided a service for cancer cases that is recognized, not only in Massachusetts but all over the country, as of the very highest grade, both in respect to its equipment and to its professional staff as well. With the additional resources which become available today, its position as one of the foremost cancer hospitals in the country is assured.

Under the wise direction of the Commissioner, and with the approval and support of the Governor and the Legislature, the service of this hospital has been made available, not only for the alleviation of advanced cases of cancer, but for the early diagnosis and effective treatment of early cases as well. This object is accomplished through the clinic for ambulatory cases maintained at Pondville, but it is supplemented most effectively by the organization of sixteen state-aided clinics in general hospitals distributed throughout the state. In the case of these clinics the approval of the local medical profession has wisely been made an essential requirement before any organization was attempted. As a result of this stipulation the interest and coöperation of the local medical profession in the maintenance of the efficiency of the clinic and in the reference to it of suspicious cases has been secured.

Through the permanent organization of the Department of Public Health a close coöperation has been maintained between these clinics and Pondville, and especially through the social service department the reference of suitable cases to Pondville for admission and treatment, and the follow-up of cases after discharge, back to the clinics, is facilitated.

As a result of the establishment of these institutions by the state, the advanced cancer case in Massachusetts is able to secure appropriate and effective palliative treatment, and the early case of cancer, rich or poor, can receive expert service to provide a prompt and accurate diagnosis, and can be given that treatment, whether by radiation or by surgery, which is best adapted to his individual case. Through the participation of the local medical societies throughout the state, the provision of these additional resources for the diagnosis and treatment is widely known, and a more accurate knowledge of the essential facts in regard to cancer, a greater alertness to observe suspicious symptoms and a disposition to avoid delay and to procure the immediate settlement of the question of diagnosis by reference of the patient to a special cancer clinic is already manifest. It will be indeed surprising if the benefits of these resources do not soon begin to make themselves evident by a diminishing mortality rate in place of the steadily increasing death rate for cancer which has been recorded in Massachusetts in the past twenty years.

RELATION OF THE TECHNICIAN TO THE PATHOLOGIST

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THE pathologist and the technician are, in many respects, mutually dependent. The pathologist expects, and should receive from his technician, carefully fixed, cut and stained preparations if accurate diagnoses are to be rendered promptly.

In presenting this brief note I shall recall some observations made while enjoying an association of nearly thirty years with a pathologist. If I have learned anything worth while, let me pass it on to my fellow technicians in

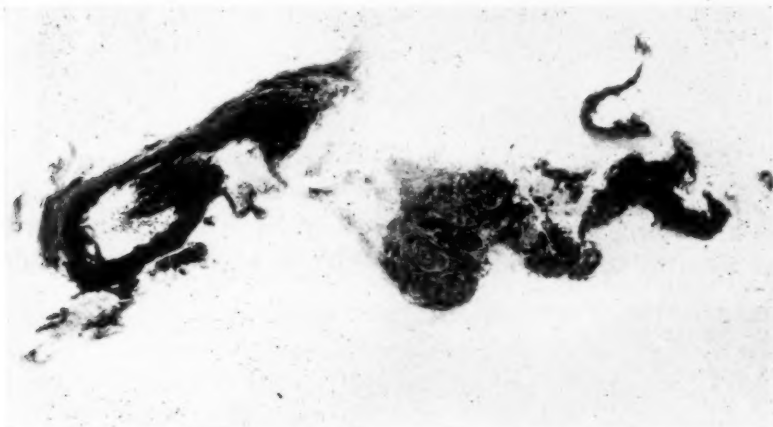


FIG. 1.—Speck of tissue less than 1 millimetre in diameter, imbedded in paraffin.
Diagnosis—Squamous carcinoma.

the hope that a closer relationship may be established between the laboratory assistant and his pathologist.

Pathologic histology is an interesting branch of medicine and is evidently a difficult subject to master, hence the scarcity of competent pathologists. The technician should always bear in mind that it is his function to exert his best efforts in handling the material entrusted to his care and that the diagnosis is the pathologist's responsibility. The pathologist often experiences great difficulty in making diagnoses upon the best histological preparations. His burden should not be increased by giving him poor work. There is little excuse for such poor preparations as are often encountered today, for the modern laboratory is fully equipped to render the best service.

Some knowledge of each other's field is necessary; the pathologist must know and appreciate the technical difficulties of his assistant's work while the technician should know something of the pathological properties of the tissues he handles in order that proper differentiation may be made in the

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staining of tissues. Thus he elevates himself from a mere dabbler in dyes to a valuable technical assistant.

The technician's service will be more valuable if in his early training he

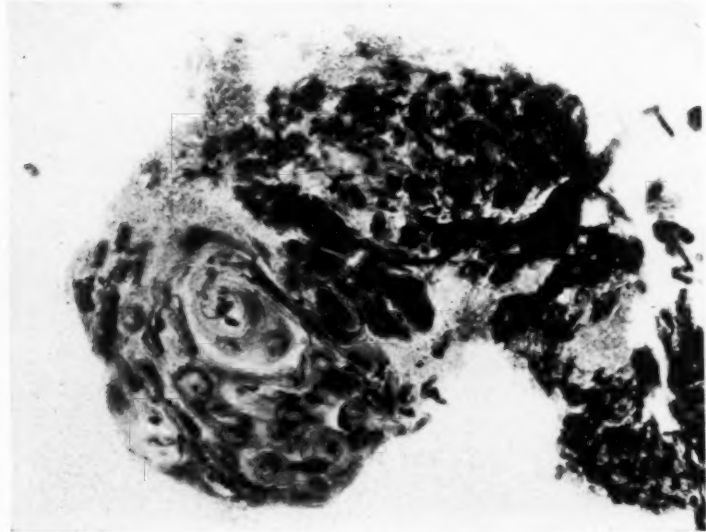


FIG. 2.—High-power magnification of Fig. 1.

secures a knowledge of normal histology. Without this he can hardly appreciate abnormal or morbid histology. Also, he will have a keener apprecia-

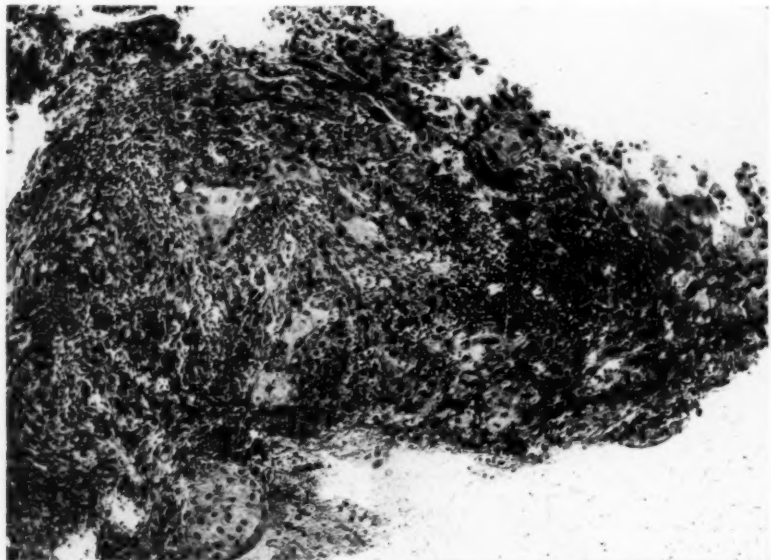


FIG. 3.—Biopsy. Tissue usually sent in for diagnosis, 1 to 2 millimetres in diameter.

tion of his work if he is present when the pathologist describes the gross material and selects the specimens to be prepared for diagnosis. In this way,

THE TECHNICIAN AND THE PATHOLOGIST

if alert, he will gain some knowledge of pathology and in turn will recognize readily the proper side of a specimen to be mounted uppermost on the block for cutting. The areas of pathological importance and their relation



FIG. 4.—Large section taken through nipple of breast; embraces entire tumor mass down to muscle.

to surrounding structures having been indicated, the final section is more likely to show the essential points. He might be warned, too, of the dangers of cutting too superficially or too deeply in the block, thus missing the areas

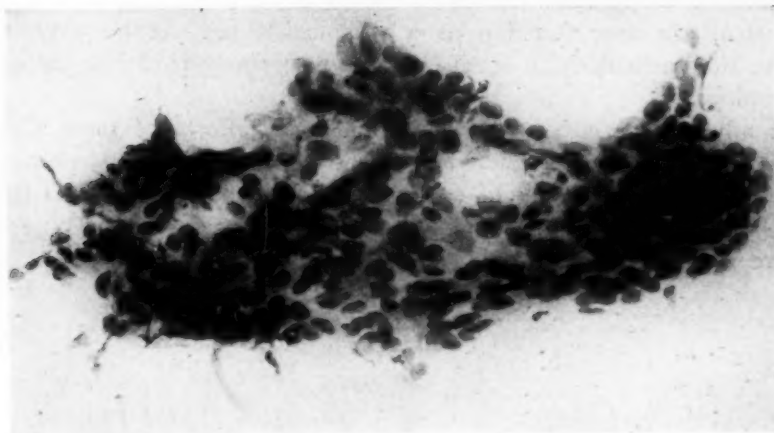


FIG. 5.—Tumor cells aspirated from a lymph-node.

of main interest. Reputations have been endangered by poorly chosen, cut and stained preparations.

The technician should strive to master not only the procedures as out-

lined in the various textbooks of pathological technic, but should learn many of the variations, "tricks of the trade" not given in the books, but learned by practical experience. There is an urgent need for shorter methods of preparation of material in order that earlier and more accurate diagnoses may be made. These demands should appeal to the imagination of the competent technician, impelling him to invent new methods in which the time of preparation is cut down.

The extreme demands of tissue preparation are aptly demonstrated by the accompanying illustrations. In one instance (Figs. 1 and 2) we had to deal with a speck of material hardly one millimetre in diameter. Yet from this tiny bit of tissue, a positive diagnosis was obtained, demonstrating that no specimen is too small when properly selected and carried through to afford a positive opinion. Extremely large sections are now available (Fig. 4) since the method of Sir G. Lenthal Cheatle has been adopted. These show the whole picture of the disease process and its relation to the adjacent parts.

Recently we have aspirated material from suspicious areas in breast, prostate and lymph-nodes, from which we make thin slide smear preparations as for blood examination (Fig. 5). These aspirations, when properly prepared, are often the means of securing a diagnosis where a biopsy was found impractical and unsafe. Of course, the method has its limitations as have many others, but when one keeps in mind the original intent of its application, *i.e.*, the differentiation between inflammatory and neoplastic processes, its application is justified because of its simplicity and rapidity.

There are isolated instances in which the technician, by virtue of a long and close association with the pathologist, may develop considerable diagnostic ability, and in the absence of the pathologist be called upon to demonstrate the gross and microscopic material to the hospital staff, thereby increasing the value of his services. I do not desire to leave the impression that the technician, can ever function as a pathologist, but yet he may render definite aid, particularly in small hospitals where only part-time pathologists are employed.

In any work which requires the intelligent efforts of more than one person, teamwork is essential and the success attained is directly proportional to the spirit and the degree of coöperation. With these conditions fulfilled, the relationship is that of a smoothly working unit whose main object is to procure for the patient an early, accurate diagnosis.

II

CANCER RESEARCH

- GEORGE A. SOPER, PH.D. Great Neck, L. I.
Formerly Director of American Society for the Control of Cancer.
"A Plea for the Encouragement of Epidemiological Research."
- DALLAS B. PHEMISTER, M.D. Chicago, Ill.
Professor of Surgery, University of Chicago.
"Undifferentiated Round Cell Sarcomas with Five-Year Cures."
- RICHARD MEAGHER, M.D. Boston, Mass.
Peter Bent Brigham Hospital.
"Concerning Intracranial Carcinomatous Metastases."
- FRED W. STEWART, M.D. New York, N. Y.
Associate Pathologist to the Memorial Hospital.
"An Analysis of the Lymphadenopathy Question with Special Reference to Hodgkin's Disease and Tuberculosis."
- ALFRED SCOTT WARTHIN, PH.D., M.D., LL.D. Ann Arbor, Michigan
Professor of Pathology and Director of the Pathological Laboratories in the University of Michigan.
"The Genetic Neoplastic Relationships of Hodgkin's Disease, Aleukemic and Leukemic Lymphoblastoma and Mycosis Fungoides."
- ELISE S. L'ESPERANCE, M.D. New York, N. Y.
Assistant Professor of Pathology, Cornell University Medical College.
"Studies in Hodgkin's Disease."
- BURTON T. SIMPSON, M.D. Buffalo, N. Y.
Director of the New York State Institute for the Study of Malignant Disease.
"Failure of Tuberculin, Karkinolysin, and Some Inorganic Compound in Therapy of Spontaneous Mouse Cancer."
- J. MAISIN, M.D. Louvain, Belgium
Director of the Cancer Institute.
"Susceptibility and Resistance to Tar Cancer, an Experimental Study."
- FRANK E. ADAIR, M.D. New York, N. Y.
Attending Surgeon to Memorial Hospital.
"Treatment of Carcinoma with Mustard Gas: A Laboratory and Clinical Study."
- FRANCIS CARTER WOOD, M.D., D.Sc. New York, N. Y.
Director of the Institute of Cancer Research, Columbia University.
"Animal Tumors as Therapeutic Reagents."
- OTTO WARBURG, M.D. Berlin-Dahlem, Germany
Director of Kaiser Wilhelm Institute for Biology.
"Mechanismus der Methylenblauatmung."

A PLEA FOR THE ENCOURAGEMENT OF EPIDEMIOLOGICAL CANCER RESEARCH

BY GEORGE A. SOPER, PH.D.

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I THINK we do not realize how much we owe to epidemiological research nor appreciate what a great deal could be learned from this kind of investigation if only it could be pursued with ability and encouragement, such as are directed to other branches of cancer study.

Some of the most important facts known about cancer are of an epidemiological character. One of these is that the cancer process, or closely related phenomena, occur throughout the animal kingdom and bear a strong resemblance to abnormal growths in the plant world. Another is that some form of chronic irritation usually precedes the appearance of a cancer.

Many suppositions which are constantly taken as proved facts and serve as ground for action await confirmation or disproof by the epidemiologist. One of these is that cancer is not infectious. Another is that the death rate is increasing. Still others are the belief that the cancer death rate is higher in some cities than in others, higher in some countries than in others, higher in northern than in southern regions, and higher among some races than others. We actually know little about these matters today. There can be no doubt that many of them could be made to give up their secrets to scientific epidemiological research.

A large field of epidemiological research with distinctly practical applications lies open in the study of cancer in industry. Not much has been done to cultivate this field so far. The promise which it offers to workers in the United States is a brilliant one.

Little is known statistically about the incidence of cancer apart from the mortality, and as official mortality rates are generally inaccurate, the prevalence of cancer anywhere in the United States is largely a matter of guesswork.

The circumstances attending the onset, and, in fact, a great deal about the progress of early cancer, as distinguished from the advanced cancer which first comes to medical attention, are obscure and not likely soon to be made clear by chance observations such as have thus far contributed most of the information which exists on this subject.

Epidemiological research of the right sort is capable of clearing up many of these points in the future as partial investigations and pronouncements of the wrong kind have done so much to obscure the truth about them in the past.

Statisticians, often with no knowledge or concern as to the accuracy of their fundamental data, but interested chiefly in compiling tables, have pub-

lished figures and based opinions on them which are seriously misleading as to cancer mortality. One country has been compared with another, one region with another, and cities have been classified according to these assumptions of cancer mortality. The effect is to obscure the truth about cancer.

Under the best circumstances which now obtain, the official general cancer mortality statistics which are compiled by our cities and states are seriously in error and in the hope of emphasizing the need of giving proper epidemiological attention to this topic a few words about these rates may be appropriate.

Nearly all the states publish rates which are known to those who are acquainted with more correct methods as "crude" rates. They are compiled by multiplying the number of cancer deaths reported during the year by 100,000 and dividing the product by the estimated mid-year population. Forty-two of the forty-eight states, including the cities within them, and twenty-one cities in states whose vital statistics are too incorrect for use, are included in what the United States Government calls the Registration Area in the continental part of the United States. The registration area is not fixed; it has increased from time to time since 1880, when it was established. In 1927, it included 91.3 per cent. of the population, or 108,327,000 persons.

The United States Census Bureau, which regularly publishes the mortality rates for the registration area and has given a great deal of careful attention to the subject of cancer, has recalculated the cancer death rates and in doing so has made certain corrections which show that the crude rates as published by the cities and states are misleading. It has made allowance for inequalities in the proportion of males and females in the population and for the number of persons present in each age group, it being known that cancer exacts a higher toll among women than men and among old people than young ones. The resulting tables of "adjusted" rates, as they are called, show much smaller differences among the cities and states than the crude rates indicate.

Thus, Vermont's rate falls from 131.7 to 89.6 and Albany's from 182.4 to 143.1, while Louisiana's rises from 67.9 to 85.6 and Detroit's from 78.4 to 108.5 per 100,000 population. Changes were made in the official rates of practically all the states and cities.

The highest and lowest crude rates in 1927 were, for the states, Maine, 137.2, and South Carolina, 41.2. The highest and lowest adjusted rates were, New York, 114.5, and South Carolina, 57.0. In the first case the difference was 96.0 and in the second, 57.5.

Smaller differences between the maximum and minimum rates also were found among the cities when the adjusted rates were compared than when the crude rates were considered. For example, the crude rate for Albany was 182.4, and for Norfolk, 55.2, whereas the adjusted rate for Albany was 143.1 and for Norfolk, 68.7. The greatest difference between the crude rates was 127.2 and between the adjusted rates, 74.4.

ENCOURAGEMENT OF EPIDEMIOLOGICAL RESEARCH

Other tables of mortality rates have been prepared by the Census Bureau in which allowance has first been made for the actual residence of the deceased before the adjusted rates have been calculated, with the object of allowing for the fact that a certain number of patients go to some other city or place for medical, hospital or institutional care and die away from home. These "refined" rates, as they are called, still further alter the order and range of the inequalities among the states and cities and show that the adjusted rates do not afford information from which correct inferences may be drawn, as to the relative mortality from cancer.

Among the states, the highest refined rate in 1927 was, for New York, 113.2, and the lowest, for North Carolina, 63.5. The difference between these extremes was 49.7. Among the cities the highest refined rate was for New York, 136.0, and the lowest, for Norfolk, 56.3. The difference was 79.7.

The refined rates show that the crude and adjusted rates are misleading, but it is probable that they are not right themselves. Nobody knows how near the truth they are. Is it likely that the true cancer death rate is 78 per cent. higher in New York State than it is in North Carolina, or 141 per cent. higher in New York City than in Norfolk? If so many more people are dying of cancer in New York in proportion to the population than are dying in the southern cities, it is of the utmost importance to learn why. If this difference is only apparent and not real, the errors should be discovered and removed. Apparently there is a considerable difference even if it has not been measured exactly. What is it due to? Would it not be desirable to see what a well-trained epidemiologist could find out about this matter?

Any rate is correct only in so far as the fundamental data upon which it rests are correct and if the underlying information as to the cause of death, residence, age or sex is not exact or the age or sex distribution of the population is not properly determined no calculation will yield a correct result. It would seem that all the errors inherent in the crude rates had not been eliminated in the refined rates. This is no reflection upon the Census Bureau or upon any person or body. The Bureau is deserving of the highest praise for the numerous studies it has made of cancer statistics. Its work surpasses that of most countries. We are simply faced with a situation in which scientific epidemiological work is called for. The study needs to be carried into the field.

Let us consider for a moment the completeness and accuracy of the original returns which go to make up the cancer statistics of our cities, states, and the general government.

Aside from the omission of a death certificate altogether, there are three principal factors which tend to make the registration of a death from cancer inaccurate: mistakes in diagnosis, mistakes in making out the death certificate, and attempts to hide cancer as the cause of death out of consideration for the feelings of the family of the deceased. It is a matter of opinion

how far these factors operate and the extent to which they influence the returns. Some persons think the reports are fuller and more correct in certain parts of the United States than they are in others. It seems futile to argue about it. The question ought to be settled through epidemiological research.

As to diagnosis, one need go no further perhaps at the present moment than to recall the fact that cancer is often mistaken for other conditions and that these may be set down as the cause of death. Cancer may fail of recognition even at the time of death in large, well-equipped hospitals where every facility exists for diagnosis. In large cities the mistakes have been found through autopsy to run as high as 30 or 40 per cent. Through the country, and especially in private practice and where the deceased has had little or no medical attention, the mistakes must be much more numerous.

How far, then, official cancer death rates are to be depended on, where they are in error, and how the mistakes can be corrected should be determined by epidemiological study.

So much confusion appears to exist between the terms statistical and epidemiological research that this brief contribution will be closed with a few words intended to point out the difference between these two methods of investigation as they appear to me.

Statistical research is essentially mathematical. Collections of numerical data are made and arranged in various ways. These may be calculations of averages, percentages, trends, norms, probable errors, and so on. Tables and curves illustrate these results. Interest centres on the information which can be extracted from a study of the figures. The gathering of the data receives less attention. Statistical research is essentially a closet study.

Epidemiological research may or may not make use of statistics. Much attention is given to the collection of the data. The investigator must have a considerable knowledge of the disease investigated. He gathers detailed information on a great many topics and as carefully weighs it. His is usually, but not invariably, a field study. He makes use of whatever method of investigation promises to give him reliable results. His aim is to help point the way to prevention and cure. He is vitally interested, therefore, in the thing studied.

There are two distinct kinds of epidemiological investigation which should be noted: extensive and intensive. Extensive work usually employs large arrays of figures and seeks to arrive at conclusions through the study of readily recognizable and measurable conditions of wide application. Intensive epidemiological research may be carried on with a very few cases. It is the penetrating character of the investigation which is directed at a small number of characteristic cases which brings out the desired information in intensive epidemiological work.

Both are needed in cancer research. I believe there is no other field of investigation which, with proper encouragement, is capable of producing results of comparable value.

UNDIFFERENTIATED ROUND-CELL SARCOMAS

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FOR many years the usual teaching in connection with malignant tumors was that the less differentiated the cell, the more malignant the tumor, the earlier it gives rise to metastases, and the worse the prognosis. It has been held particularly for carcinomas, and Broders¹ has classified them into four types according to their morphology which correspond roughly to their degree of malignancy. While this may be true for tumors in general, all four assumptions merit criticism for particular types of tumors. Thus, Borst² points out that certain highly differentiated tumors presenting a histological picture approaching mature tissue may behave like malignant neoplasms. Sarcoma presents exceptions to the rule oftener than carcinoma and there is perhaps no better example than is offered by the undifferentiated round-cell sarcoma met with most frequently in connection with the bones and the connective tissues of the soft parts of the extremities. Five cases which occurred in adults came under my care during the period of 1919-1925, and all five are alive and free from signs of recurrence at the time of writing, July 1, 1930; one for ten years and nine months; one for eight years and three months; one for seven years and two months; one for six years and four months; and one for four years and eight months. Exceptions to one or more of the rules enumerated were shown by all five tumors. Four of them were entirely undifferentiated consisting of round or polyhedral cells and almost entirely devoid of stroma except for the blood-vessels. One tumor showed organoid character in that it possessed a connective-tissue stroma in places. Two of the tumors increased in size rapidly, while two increased slowly after the detection of the initial swelling. All of the tumors were treated before they were of sufficient size to produce cachexia, although one of them had reached dimensions that were compatible with it. In no instance was there evidence of metastases nor have metastases developed since treatment was initiated. The prognosis in this type of case has been greatly modified by the use of irradiation therapy, since the group ranks among the most radiosensitive of tumors. However, the largest tumor of the group was treated by amputation, which emphasizes particularly the fact that metastases may be absent although the disease is advanced. The therapy employed in these cases was extremely varied. In one case it consisted of amputation only; in one case it consisted only of irradiation by means of radium and X-rays; while in two cases it consisted of X-ray irradiation followed soon by excision and radium implantation with subsequent X-ray irradiation. In one case the tumor disappeared under X-ray irradiation, after which the bone in which it had developed was excised and further X-ray irradiation

was employed. It is interesting in view of the fear entertained by many, of spreading metastases through operative interference, that biopsy was performed in four cases; that in one case there was an extensive regional excision eighteen months previously followed by a prompt recurrence; that in two cases there was apparently incomplete local removal after pre-operative X-ray irradiation; and that in one case there was a pathological fracture of the involved bone one month before the patient was seen and that a biopsy was performed one week before the beginning of the irradiation.

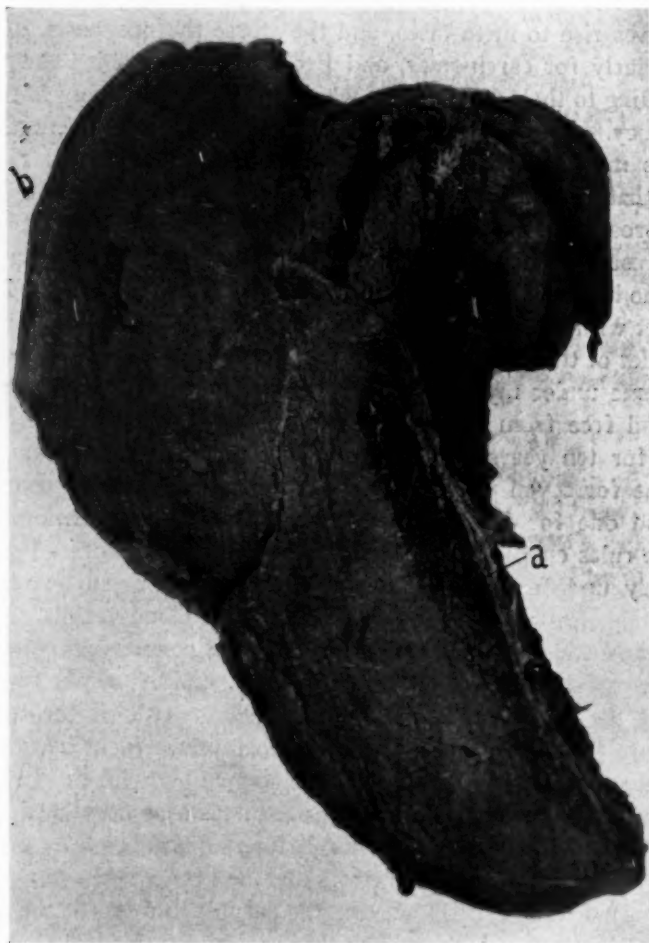


FIG. 1.—Case I. Sagittal section of scapula and tumor. Infraspinatus muscle (a), skin (b).

CASE I.—Male, aged twenty-nine, was seen because of a large swelling of the dorsum of the right scapula which had developed during the previous seven months. At first the swelling was symptomless, but recently it had produced some pain and considerable limitation of motion in the shoulder. No loss in weight or strength. Examination showed a large, firm, soft, oval swelling involving the entire posterior scapular region and limiting elevation of the arm. General condition of patient excellent. No enlargement of axillary or cervical glands. Röntgenogram of right shoulder negative for bone change. Röntgenogram of chest was negative for lung metastases.

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Operation.—Intrathoracoscapular amputation. Pathological examination revealed a grayish, soft, oval tumor which occupied the entire posterior scapular region (Fig. 1). It came into contact with the bone above and was separated from it below by the infraspinatus muscle. The tumor protruded forward between the glenoid and coracoid process making an egg-sized mass extending into the axilla. It produced little bony erosion where it was in contact with the upper portion of the bone. The muscles of the region were extensively invaded by the tumor and at the level of the spine of the scapula it infiltrated the deeper portions of the skin.

Microscopic examination showed the entire tumor to be extremely cellular. It was

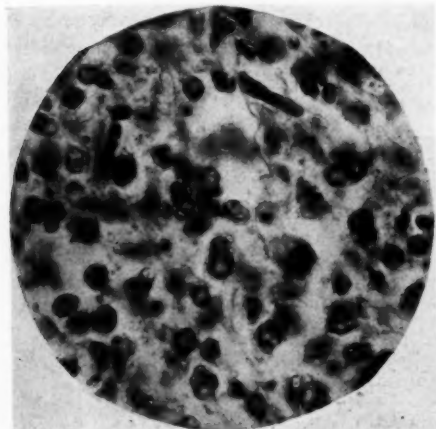


FIG. 2.—Case I. Magnification 625 diameters.

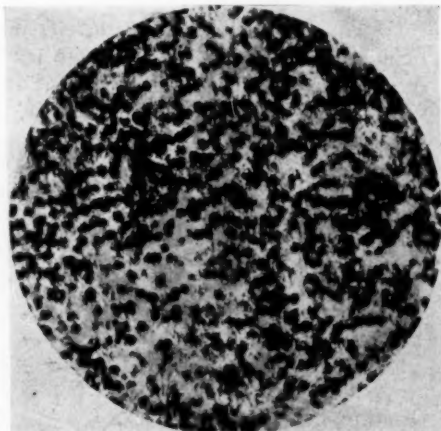


FIG. 3.—Case II. Magnification 300 diameters.

composed largely of medium-sized round cells with more or less irregularly shaped nuclei. Hyperchromatic nuclei were common but mitotic figures were scarce (Fig. 2). There was practically no intercellular substance present aside from blood-vessels. Sections from a deeper portion of the tumor showed much necrosis.

Diagnosis.—Paraosteal undifferentiated round-cell sarcoma.

Post-operative Course.—There was an uneventful recovery from operation and the patient has remained entirely well and free from signs of recurrence up to now, ten years and nine months after operation.

CASE II.—Female, aged forty-four. Two years and three months before examination patient had noticed a soft swelling on the lateral aspect of the right arm above the external condyle. It increased slowly in size and eighteen months later was excised and found to be a sarcoma. A small amount of X-ray treatment was given but the lesion recurred and had gradually increased in size. Examination revealed nothing abnormal aside from the right arm. There was an oval mass 12 centimetres long by 6 centimetres wide occupying the anterior and lateral aspect of the lower portion of the right upper arm. It was soft, fixed, and extended from subcutaneous tissue to the bone. A röntgenogram of the humerus was negative for bone changes and there were no signs of metastases in röntgenograms of the chest.

A pre-operative massive deep X-ray treatment was given with a 200,000-volt current delivering $\frac{4}{5}$ of an erythema dose. One week later the tumor was excised locally. It extended from subcutaneous tissue to bone and was soft and grayish in color, infiltrating the muscles and surrounding the radial nerve which was excised. Tumor was broken into at operation and was curetted off of the front of the humerus, the removal being evidently incomplete. Eight needles containing $12\frac{1}{2}$ milligrams each of radium were implanted in the field, four of them in contact with the supracondylar portion of the humerus in front. They were removed in ten hours.

Microscopic examination of the excised tumor showed it to consist of large round cells

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which were well preserved in the narrow peripheral portion but which were extensively necrotic in the central portion. There was practically no stroma throughout the tumor (Fig. 3). Irregular mitoses and hyperchromatic nuclei were occasionally to be seen.

Post-operative Course.—The wound healed with a slight serous discharge which persisted for two weeks. Four months and eight months later the patient received $\frac{1}{2}$ of an erythema dose of deep X-ray therapy to the region. Sixteen months later a mild acute inflammation developed in the field, leading to the formation of a discharging sinus that healed after two weeks. The patient has since remained well and there have been no signs of local recurrence or metastases up to the present time, eight years and three months after operation.

Radium Necrosis of Humerus.—A very interesting change was that produced by the radium which came into contact with the front of the humerus. It was left *in situ* long enough to produce an extensive area of necrosis. The dead bone subsequently underwent sequestration but it was at an extremely slow rate as compared with the sequestration



FIG. 4.—Case II. Sixteen months after radium exposure at (x). No sign of absorption or sequestration of bone killed by radium.

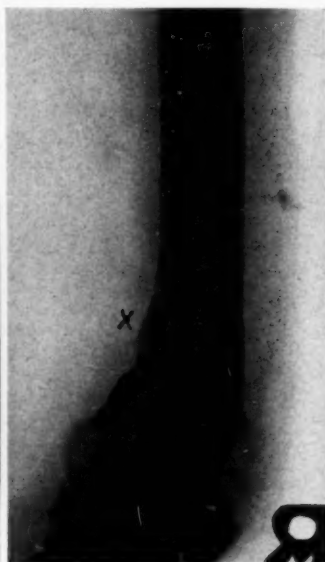


FIG. 5.—Case II. Three years and ten months after radium application, showing beginning absorption of radium. Dead bone (x).

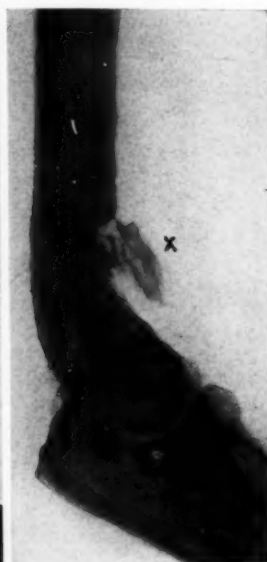


FIG. 6.—Case II. Sequestration of dead bone (x) complete eight years and two months after radium exposure.

of bone that is killed as a result of pyogenic infection. A röntgenogram taken sixteen months after operation and radium implantation revealed no change in the humerus at the seat of radium exposure (Fig. 4). A röntgenogram three years and ten months after the operation revealed evidence of irregular absorption of bone in the anterior supracondylar region, but no sequestration (Fig. 5). A röntgenogram taken five years and ten months after operation showed further absorption and sequestration almost complete with compensatory new bone formation along the posterior surface of the humerus at that level. A röntgenogram taken eight years and two months after operation revealed complete sequestration of the dead bone which had become slightly displaced from its bed anteriorly (Fig. 6).

The extremely slow rate of sequestration and absorption of the dead bone was due undoubtedly to the fact that the surrounding tissues which had to do the absorbing were radium burnt and consequently reacted very sluggishly. The presence of a slight, low-grade infection probably had something to do with the fact that the dead bone was

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sequestered rather than replaced by creeping substitution as was found to be the case in experiments³ when bone killed aseptically by radium functions in the support of the extremity and as was observed in Case V of this series.

CASE III.—Female, aged thirty, complained of a gradually increasing swelling of the right deltoid region of six months' duration. Two months previously it had been biopsied and pronounced sarcoma. The swelling had gradually increased in size but there had been no local or general disturbance. Eleven years previously the head of the right humerus had been resected because of a chronic arthritis of the shoulder, the nature of which was unknown. Since then the shoulder had been symptom free, but was markedly restricted in motion. Physical examination was negative aside from the right shoulder region. There was a large, tense, soft, oval swelling in the region of the right deltoid muscle which measured about 12 centimetres in its longitudinal axis. Marked fixation of shoulder-joint. A röntgenogram revealed absence of head of humerus but no sign of erosion of the side of the shaft in the region of the soft-parts swelling. A second biopsy was performed which revealed an extremely cellular, small, round-celled tumor that contained almost no stroma and a few blood-vessels (Fig. 7). There were many polyhedral cells and a fair number of mitotic figures.

Diagnosis.—Paraosteal undifferentiated round-cell sarcoma. Two massive X-ray treatments were given one week apart, one front and one back, comprising an erythema dose. Tumor began to slough out through the biopsy incision. Two weeks later the tumor was excised locally. It lay beneath and invaded the deltoid and came into contact with the bone. It was cut into and scooped out, after which the walls were cut away. Apparently an incomplete removal was accomplished. Twelve needles each containing 12½ milligrams of radium were implanted in the field and left for twelve hours. One month subsequently she received ¾ of an erythema dose of massive deep X-rays. This was repeated three weeks later. The wound was moderately infected but gradually healed in the course of two months. The patient has remained in good health and free from evidences of a recurrence up to now, six years and four months after the operation. Although radium came into contact with bone, so far there has been no sign of sequestration of the dead bone.

CASE IV.—Male, aged thirty-three, sustained a fracture of the outer third of the right clavicle as a result of lifting thirty-seven days before examination. The arm had been kept bandaged to the side but slight pain had continued at the seat of fracture and a swelling had appeared gradually. Examination revealed a firm, oval, soft swelling, centring at the junction of the outer and middle thirds of the clavicle, which extended both above and below the bone for a distance of about 7 centimetres. A false point of motion could be elicited in the clavicle at this point. A röntgenogram revealed an irregular area of destruction extending over a distance of 4 centimetres in the clavicle about the junction of the outer and middle thirds with a fracture through it and downward displacement of the outer fragment. The shadow of an oval, soft-parts tumor could be seen about it. Biopsy revealed a grayish, soft tumor about 2 centimetres thick covering the bone. Microscopic examination showed the tissue to be composed of densely packed round cells and of a smaller number of polyhedral cells of uniform size. There were numerous capillaries throughout the tumor and but little necrosis. There were many hyperchromatic nuclei and very few mitotic figures. No bone or other type of stroma

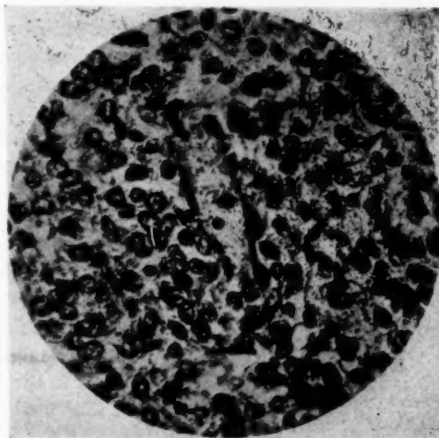


FIG. 7.—Case III. Paraosteal sarcoma of subdeltoid region.

Diagnosis.—Undifferentiated round-cell sarcoma of the clavicle with pathological fracture.

Röntgen-ray therapy was started one week later. A series of eight regional treatments was given at the rate of three per week using 140,000 kilovolts and delivering altogether 5/7 of an erythema dose. Two months later two treatments of massive deep X-ray were given front and back at two-week intervals delivering an erythema dose. Under treatment the mass gradually disappeared and the fracture became firm although röntgenologically an irregular, broad line of reduced density at the seat of the intermediary callus could still be seen. Because of the possibility that tumor might be retained within the bone the outer 4/5 of the clavicle including soft parts about the old region of tumor was excised four and a half months after the biopsy. No tumor was seen grossly about



FIG. 8.—Case IV. Section of excised clavicle showing disappearance of tumor and the cartilaginous intermediary callus of pathological fracture.

the seat of fracture at which point there was an irregular, spindle-shaped swelling. Longitudinal section of the bone revealed a broad, irregular, cartilaginous intermediary callus at the seat of fracture and grayish necrotic tissue in the marrow cavity of the mesial fragment (Fig. 8). Microscopic sections of the entire extent of the previously involved clavicle revealed signs of an old healing fracture but no traces of tumor could be found. There was some necrotic bone and cancellous debris in the end of the mesial fragment. Sections of the surrounding soft parts revealed scar tissue and muscle but no traces of tumor. The patient has remained well and free from signs of recurrence during the four years and four months since the operation or four years and eight months since Röntgen-ray treatment was started.

In this case both the pathological fracture and the biopsy might be regarded as factors that would predispose to the development of metastases and still none have so far made their appearance.

CASE V.—Female, aged fifty-six, complained of pain in the left sciatic region for nine months and a limp and swelling in the region of the left ischium for five months. Examination revealed an elderly woman in good general health. There was a soft mass in the region of the body of the left ischium, bulging both laterally and mesially and approximately 10 centimetres in diameter. Examination otherwise essentially negative. A röntgenogram revealed extensive, irregular reduction in density in body and ramus of the left ischium. Biopsy revealed a firm, grayish tumor mass. Microscopically it consisted of masses of small round cells which in regions were separated

by irregular bands of immature connective tissue giving the tumor an organoid appearance. There were numerous hyperchromatic nuclei among the round cells with few mitotic figures. No mitoses were seen in the connective tissue portions. Blood-vessels were fairly numerous throughout the section. A diagnosis of undifferentiated round-cell sarcoma of the ischium was made and the lesion was treated entirely by irradiation. Eight needles containing each 12½ milligrams of radium were introduced by means of spikes and left for thirteen hours delivering 1300 milligram hours. The procedure was repeated in four weeks. Following this four series of eight regional X-ray treatments were given with an interval of two months between 5/7 of an erythema dose being given during each series. The tumor and symptoms disappeared under treatment and subsequent radiograms showed re-ossification of the ischium. She has remained free

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from physical and X-ray evidences of recurrence for seven years and two months since treatment. There have been occasional pains in the hip from time to time and the patient was complaining when last examined but radiograms have shown no evidence of recurrent destruction of bone and no signs of pulmonary metastases. The bone killed by radium has not been sequestered. Her general health is good. Because of these symptoms there is more reason to doubt a permanent cure in this case than in the others.

The degree of differentiation of these tumors was so slight that it was impossible to state the type of tissue to which they belonged. Some would no doubt classify them as Ewing's endothelioma, but three tumors arose outside of bone in locations where endothelioma rarely develops. It is difficult to estimate the value of the local excision employed in the three cases with irradiation therapy. In Cases II and III where it was preceded and followed by irradiation, large amounts of tumor were removed, and only scattered bits left behind; consequently the body had less tumor to resist and irradiation less to overcome and there can be little doubt that this creates an advantageous situation. Failure to find tumor cells histologically in the excised clavicle in Case IV is no proof that there might not have been a recurrence had it been let alone.

SUMMARY

Cures lasting from four and two-thirds to ten and three-fourths years have been obtained in five cases of undifferentiated round-cell sarcomas, two of which began in bone and three in the connective tissues about bone. Biopsy performed in four cases, a pathological fracture in one and a previous incomplete operation in one did not lead to metastases. This experience favors the view that biopsy is not a dangerous procedure. One tumor was treated by irradiation only, one by amputation, and three by both irradiation and local excision. Several years were required in case 2 for sequestration of the bone killed by radium used in the treatment due to the fact that the adjacent tissues which produced the absorption were radium burnt.

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INTRACRANIAL CARCINOMATOUS METASTASES

WITH NOTE ON RELATION OF CARCINOMA AND TUBERCLE

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IN ANY large series of intracranial tumors there is certain to be found a definite percentage of metastatic carcinomas. Many of these are readily predictable following careful examination of the breast, and of late years the more routine use of chest plates has shown the true place of the lung as an unsuspected and often otherwise undemonstrable source of primary cancer. The infrequency of coexisting multiple primary intracranial tumors of different types, there being only four such examples observed in our series, makes the appearance of bilateral or combined cerebral and cerebellar signs of great diagnostic significance. The occasional systemic manifestations, the rapid onset of intracranial signs, and the speedy downward course which many of these patients pursue frequently offer a clue to a presumptive diagnosis in spite of inability to demonstrate a primary site of malignancy. There remain, however, a certain number in which the pre-operative diagnosis is missed, and it is in the hope of further correlating our known observations that the following statistics are offered.

In a series of 1,850 verified intracranial tumors to May 10, 1930, fifty-seven are metastatic, representing 3 per cent. of the total. Of these forty-four are carcinomas, four are hypernephromas, and nine are sarcomas. This does not, of course, represent the true relation of metastatic tumors to tumors as a whole, because the prognosis of these patients, generally speaking, is so unfavorable that they are rarely deemed fit subjects for operation, and consequently many of them remain in the unverified group.

Grant,¹ in a previous report from this clinic, summarized the records of the various intracranial metastases to March, 1926. In the present study particular attention will be given to the carcinomas.

The primary site of the forty examples of carcinoma in the Brigham Hospital series is shown in the following table:

Primary focus	No. of cases	Per cent.
Breast	10	25.0
Lung	14	35.0
Mouth and sinuses	2	5.0
Liver and intestines	2	5.0
Generative organs	1	2.5
Kidney	1	2.5
Primary focus unknown	10	25.0

As may be seen from the above, lung and breast comprise 60 per cent. of the series, and are the only tumors in sufficient numbers to make general

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estimations of value. Fried and Buckley² have stressed the insidious course of primary lung cancers with suddenly developing intracranial signs, and it is impossible to judge the time of onset of the primary malignancy.

Breast carcinomas, however, since they are so frequently operated upon, lend themselves to more detailed records, and in the following table a summary of the ten cases of intracranial metastases in which the primary focus occurred in the breast is given.

Case	Age	Period from breast operation to onset of intracranial symptoms	Period from presence of lump to onset of intracranial symptoms	Survival period after intracranial operation	Survival period after onset of intracranial symptoms
1.....	61	6 yrs. 4 mos.	7 yrs. 10 mos.	(No operation)	8½ mos.
2.....	42	6 mos.	(No operation)	4 mos.
3.....	65	11 yrs. 9 mos.	(No operation)	3½ mos.
4.....	50	3 mos.	3 mos.	8 mos.
5.....	53	2 yrs. 6 mos.	1 day	6 mos.
6.....	49	1 yr. 10 mos.	2 weeks	3½ mos.
7.....	59	6 yrs. 2 mos.	3 weeks	9 mos.
8.....	30	3 yrs. 4 mos.	3 yrs. 11 mos.	5 mos.	9 mos.
9.....	50	(Duration not noted)	1 mo.	7 mos.
10.....	52	1 yr. 1 mo.	Living	Living
Average....	51	3 yrs. 10 mos.	6 weeks	6 months

In this group, the ages vary from thirty to sixty-five years, the average being fifty-one years. The longest survival period after operation is five months, the average being six weeks, while the longest survival period after the onset of intracranial symptoms is nine months. The time interval between the breast operation and the appearance of the intracranial symptoms varies widely, the shortest period being three months, and the longest nearly twelve years, an average of over three and a half years. Since tissue from the primary tumor is usually unavailable, it is impossible to hazard more than a guess as to the rôle the type or extent of the tumor plays in determining the probability of intracranial metastasis. From the diagnostic point of view no positive stand can be taken on mere time interval alone even after considering the age of the patient and histological grade of malignancy of the primary lesion. Moreover the so-called typical clinical history of very rapid progress of an intracranial lesion, often with an accompanying psychosis, cannot always be relied upon, even in cases of established breast cancer. As an example of this the following case is cited.

CASE I.—P. B. B. H. Surg. No. 35806. Admitted January 9, 1930. Woman, L. M. N., forty-eight years of age, complaining of severe headache of three months' duration. *Family history* unremarkable.

Past history.—Twelve years ago she began to have fainting spells which lasted from a few minutes to almost an hour and were unaccompanied by convulsions. Her second attack came on one year after the first, and over a period of four years she had irregularly recurrent seizures with no increase in frequency or severity. At this time she was subjected to an appendicectomy, the uterus was suspended and a small ovarian cyst was

removed. Within a year of this operation her attacks ceased save for a single lapse of consciousness five years ago. She had no further complaints and believed herself in excellent health.

Two years ago, in January, 1928, she noted a hard painless lump in the upper inner quadrant of the left breast. This gave her no concern but its persistence caused her to seek examination a little more than a year later and the mass was noted as being 4 centimetres in diameter, slightly adherent to the skin and with no evidence of axillary or supraclavicular involvement. The opposite breast was normal. On June 6, 1929, eight months prior to entry, a radical amputation was performed and although grossly no axillary extension was demonstrable, section showed a carcinoma simplex of scirrhus type, Grade II, with metastases to lymph-node. Healing was good and recovery rapid.

Present illness.—Four and a half months before entry (two and a half months after her radical breast operation), she began suddenly to have severe occipital and vertical headaches. Patient immediately thought of her eyes, but altered lenses gave no relief. The headaches continued with frequent remissions up to the time of admission and the last two months were definitely milder until one week before entry, at which time she had a very severe headache with nausea and vomiting. She had had no peripheral motor or sensory symptoms and no visual disturbances.

Neurological examination showed a very slight secondary atrophy of left nerve head without choking and no further signs whatsoever.

X-ray findings.—Skull plates disclosed a mass 9 by 9 by 7 centimetres in the right temporal region which was of markedly increased density. There were mild skull changes of increased pressure. The röntgenologist's impression was that it was a meningioma. The lungs were noted as clear.

Operation.—In view of the positive X-ray findings, operation was performed in two stages on January 31, 1930, and February 1, 1930, with removal of a meningioma rich in calcium. As removal progressed, the last remaining attachment of the mass contained the main branch of the middle cerebral artery, injury of which caused a fatal hæmorrhage. Subsequent section of the brain failed to reveal any sign of metastatic carcinoma.

Comment.—The history of sudden onset of terrific headaches, nausea and vomiting in a woman of forty-eight, who seven months before entry had a radical breast amputation for a scirrhus carcinoma of rather high malignancy with axillary metastases, strongly suggested intracranial metastasis until the routine X-ray examination disclosed a partially calcified meningioma. The case well illustrates the difficulty that may confront the surgeon in making up his mind from the clinical history alone as to the nature of the lesion he expects to find.

If this difficulty exists in the case of patients with obvious breast tumor or with the scar of a breast amputation to suggest the probability of the nature of the intracranial growth, the diagnosis of a primary carcinoma of the lung is still more obscure, the primary lesion having been recognized in only four of the fourteen cases, in contrast to 90 per cent. of correct pre-operative diagnoses of metastases from the breast.

It is the usual clinical practice to consider a syndrome of a single etiology, and when two supposedly antagonistic lesions, both capable of producing the same intracranial signs, are found in the same individual, one is faced with a diagnostic problem in which the opinion of various observers must be evaluated. Just such a situation existed in the following case.

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CASE II.—P. B. B. H. Surg. No. 35063. Admitted October 18, 1929, woman, M. G., aged thirty, with complaint of occipital headaches, failing vision, nausea and vomiting of four months' duration.

Family history.—Direct and prolonged exposure to active tuberculosis among members of her immediate family, four of whom succumbed to pulmonary tuberculosis and with whom she was associated intimately from childhood.

Past history.—In 1903, at the age of four years, she had tuberculosis of the right

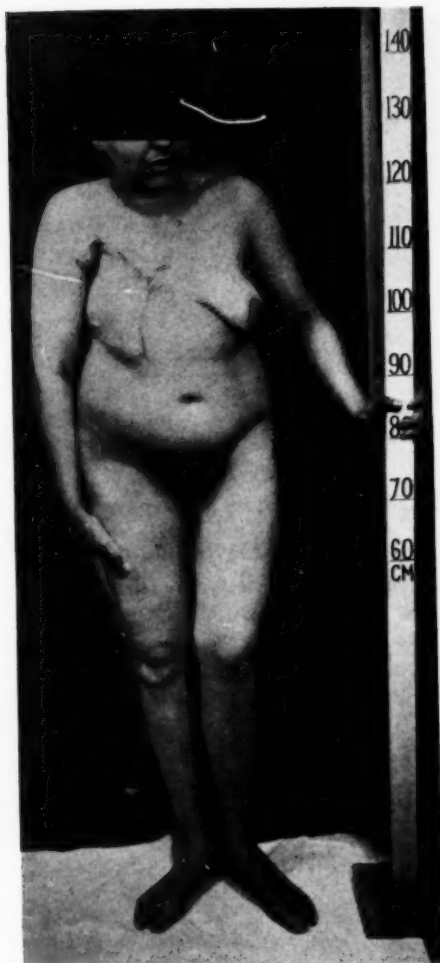


FIG. 1.—Case II. Showing scar of radical breast amputation and deformity of hip.

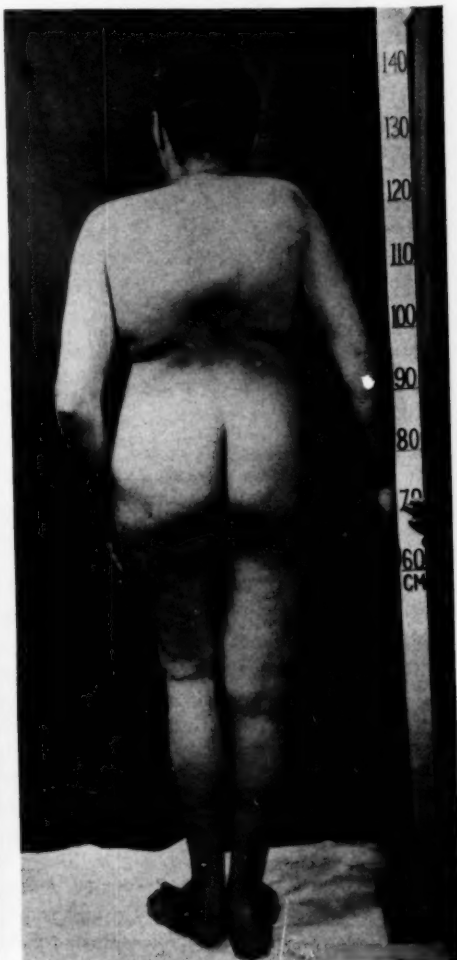


FIG. 2.—Case II. Showing marked spinal deformity. Note scars of suboccipital exploration and spinal fusion operation.

ankle with discharging sinuses, which after treatment for three years at the Children's Hospital finally healed satisfactorily.

In 1905 she began having symptoms associated with the left hip-joint, and a year later was admitted to the wards of the Children's Hospital for treatment of tuberculosis of this joint. She did fairly well under observation for the next two years until a tuberculous abscess developed at the end of that period.

In 1913, at the age of fourteen, she was admitted to the Carney Hospital with tuber-

culosis of the spine. An Albee spine operation was performed with fusion of the fourth to tenth dorsal processes.

Except for a story of "influenzal pneumonia" in 1919, the history during the next thirteen years was quite uneventful.

In 1926, at the age of twenty-seven, the patient was again admitted to the Carney Hospital, with complaint of a lump in the right breast of seven months' duration. February 18, 1926, a radical amputation of the breast was performed, with removal of a

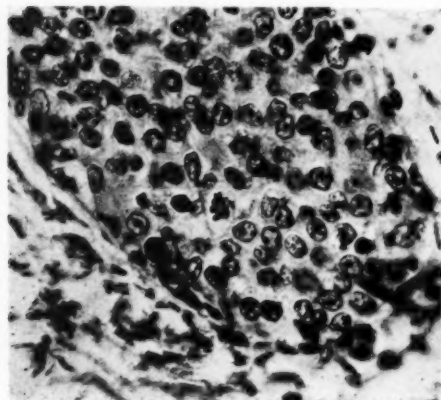


FIG. 3.—Case II. Characteristic field of scirrhous carcinoma simplex of breast. (Hematoxylin eosin stain x 600.)

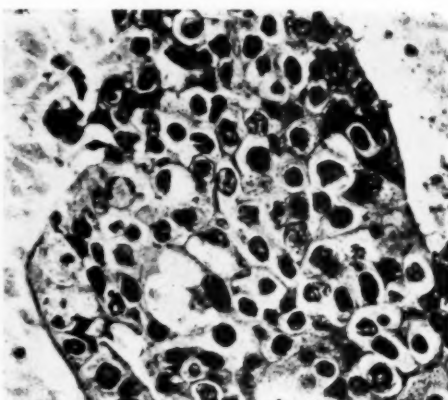


FIG. 4.—Case II. Intracerebellar metastasis of the same tumor shown in Fig. 3. The cells are much larger and there are numerous mitoses. (Hematoxylin eosin stain x 600.)

very hard nodular carcinoma in the left upper quadrant, which was adherent to the skin. There were no masses in either axilla except for one small gland in which no evidence of malignancy was found.

Present illness.—For four months severe occipital headaches associated with stiffness of the neck, nausea and vomiting; diminution in vision; irregularity of menses. For three months diplopia, persistent until two weeks before entry. Four weeks ago the patient suffered two seizures in which she lost consciousness and bit her tongue, though no clonic movements were observed. On both occasions she complained of transitory numbness of the left hand preceding the attack.

Physical examination.—The signs of her healed tuberculosis were a partially ankylosed right ankle and left hip, and immobilization and deformity of the dorsal spines with marked kyphosis (Figs. 1 and 2). The chest was free of signs, but X-rays showed evidence of old healed pulmonary tuberculosis. There was no evidence of local recurrence in the skin of breast or axilla.

Neurological examination revealed bilateral choked discs $4\frac{1}{2}$ D. right and 3 D. left. Deep reflexes were exaggerated on both sides.

Pre-operative diagnosis.—Cerebellar tumor. The localizing symptoms were insignificant except for the history of suboccipital headaches. Owing to rigidity of the leg and dorsal kyphosis, gait and station were difficult to test. Although a lesion of the posterior fossa was suspected, in view of the story of left-sided attacks a preliminary ventriculography was made, which disclosed an internal hydrocephalus.

Operation.—October 24, 1929. Suboccipital exploration with disclosure of what was regarded as a patch of tuberculous adhesive meningitis over left hemisphere, and a large subcortical tuberculoma associated with an abscess within the right hemisphere. Extirpation of tumor, which was nodular and adherent, and Zenker fixation of wall of abscess. Charring of surface involvement by coagulating current. Closure of wound in layers as usual.

Pathological diagnosis.—Metastatic carcinoma. (Figs. 3 and 4.)

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Subsequent notes.—Patient made a rapid recovery and was discharged free from symptoms on November 21, 1929. In January, 1930, she was admitted to the House of the Good Samaritan. At this time there was hemiplegia of the left side. There was gradual recurrence of intracranial symptoms, and death occurred March 12, 1930.

Comment.—The oft-recurrent tuberculosis which this girl had shown from early childhood with involvement of many sites weighed heavily in favor of a presumptive diagnosis of tuberculosis, particularly since the onset and course of her neurological symptoms so closely simulated that of the common cerebellar tuberculoma. In spite of the three-and-a-half-year interval since the breast was amputated, and the medium grade malignancy of her breast cancer, the course of such a tumor in a woman of twenty-six is ordinarily so rapidly fatal that we should doubtless have more seriously considered cancer in the differential diagnosis.

Although Van Wagenen³ has shown the dangers of disseminating meningitis following operative removal of tuberculomas of the cerebellum, the electrosurgical method now at our disposal, by means of which dissection of tissue may be carried out without dissemination of inflammatory products and with simultaneous surface sterilization and sealing off of the structures traversed, offers the surgeon great opportunity in attempting a radical extirpation of such a lesion. It was for this reason that the extirpation of the supposed tubercle was undertaken in this patient rather than leaving the operation as a decompression.

Cancer and tuberculosis.—One cannot well report a case of coincidental carcinoma and tuberculosis without some reference to the recent revival of interest in the possibility that the two diseases are antagonistic.

The first observation of the infrequent coëxistence of cancer and tubercle is ascribed to Cruveilhier, who in 1828 concluded that the relative rarity of the double lesion was due to the widely different age-groups usually attacked by the two diseases. Rokitansky,⁴ in 1846, as an outcome of his experience offered a theory heavily tinged with "humoral" concepts which postulated an antagonism between the tubercle "crasis" and the cancer "crasis." His astute observation that the primary site of cancer is rarely that of tuberculosis and that the converse is also true is unquestionably correct, but his assumption of the antagonism of the "crases" of the two diseases was immediately attacked, notably by Lebert⁵ who in 1852 flatly stated that the idea was untenable because he had many times observed the coincidence of tubercle and cancer. Paget⁶ in 1853 agreed with Rokitansky as to the antagonism of the cancerous and tuberculous "diatheses" and noted a case of a woman of twenty-five with a rapidly growing breast cancer which was surgically removed and in whom six months later both local and axillary metastases occurred with sloughing ulcerations. This situation obtained for one year and then quite suddenly healing took place, although the woman had gradually failed in strength and died two years post-operatively. At autopsy she presented extensive fulminating tuberculosis with cavitation in both apices and widespread smaller tubercles throughout the lungs in addition to fairly extensive

carcinomatous metastases in distant areas. He concluded that "the progress of the tuberculous process was commensurate with the remarkable regress of the carcinomatous extension."

The widespread influence of Rokitsky both here and abroad led to very frequent consideration of the above premise, and a precisely similar division of opinion exists today as to the frequency and infrequency of the coëxistence of the two processes, with corollary observations on the altered course of cancer when tuberculosis has been superimposed either naturally or artificially. Marked disparity in autopsy statistics on relative frequency of the diseases is explained by a failure to note the ages of the patients, the activity or extent of the tuberculosis and by failure to exhaustively search the material when once the main cause of death has been ascertained.

Bastedo⁷ in 1904 summarized the then reported cases, and showed the following distribution of primary carcinoma associated with *active* tuberculosis mainly in lung, intestines and lymph-nodes.

Breast	10	Esophagus	13
Uterus	10	Stomach	39
Cheek	1	Liver	8
Jaw	2	Pancreas	3
Tongue	1	Bowel	4
Pharynx	1	—	—
		Total	92

In addition, after excluding the well-known tendency to epithelioma formation superimposed on long-standing lupus, he collected the cases in which tuberculosis and cancer existed in the same organ with the following distribution of the lesions.

Breast	7	Stomach	3
Uterus	1	Small bowel	3
Larynx	2	Large bowel	4
Lungs	20	Liver	2
Esophagus	4	Rectum	3
		—	—
		Total	49

Moak's description⁸ of carcinoma of the prostate in a case of pulmonary tuberculosis with subsequent distant involvement of lung, bronchial lymph-nodes, adrenal, liver and spleen by both processes, and Warthin's⁹ report of a breast cancer with axillary metastases into a node already the seat of active tuberculosis show clearly the ability of cancer metastases to flourish in soil already involved in tubercle formation. The literature contains a great number of similar isolated reports and Broders¹⁰ from his own material showed twenty cases of coëxistence of active tuberculosis and cancer, in six of which the two processes were to be observed in the same microscopic field.

The observations recorded above would appear to indicate that the two disorders coincide sufficiently often to show that there is no specific antagonism. Nevertheless, believing such an antagonism to exist, there have been

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made isolated attempts to tuberculinize patients with carcinoma considered hopeless from any other therapeutic viewpoint. McCaskey,¹¹ in 1902, was the first to suggest this and, although citing possible improvement in one case, gave no detailed report. Dabney¹² in 1916 again attempted this method of therapy, and of six patients injected, noted marked improvement over a three-month interval in a young woman with an oesophageal cancer. No further clinical attempts were carried out until Delbet and Monod in 1920,^{13, 14} in a fairly extensive and carefully conducted series of cases studied the thermal reactions in various types of cancer patients with graduated doses of tuberculin. In addition they studied the effect of tuberculin injected locally into cancer tissue, but were unable to demonstrate in either procedure any conclusive findings save the expected thermal rise. More recently statistical studies of post-mortem material have led biometricians¹⁵ to feel that an antagonism was demonstrable between the two processes, and in consequence still another attempt has been made by Pearl, Sutton and Howard¹⁶ to tuberculinize carcinoma patients in the hope of altering the progress of the malignancy.

CONCLUSIONS

1. Of 1,850 verified intracranial tumors fifty-seven (3.0 per cent.) are metastatic, and of these forty-four (2.3 per cent.) are carcinomas.
2. Of forty-four metastatic intracranial carcinomas, one-fourth are primary in the breast.
3. The average age of patients with intracranial metastases from the breast is fifty-one years, the oldest being sixty-five, and the youngest thirty years old.
4. The onset of intracranial signs after primary focus in the breast averages over three and a half years, the interval ranging from three months to twelve years.
5. The course from the appearance of intracranial symptoms is rapid, fatality ensuing on an average of six months, and operative interference is survived on an average of six weeks, the longest period being five months.

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AN ANALYSIS OF THE LYMPHADENOPATHY QUESTION
WITH SPECIAL REFERENCE TO HODGKIN'S
DISEASE AND TUBERCULOSIS

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ANY precise knowledge concerning the interrelations which many pathologists maintain exist in the group of diseases of the lymphatic apparatus must necessarily await sufficient etiological investigations to afford a sound basis for judgment. To the clinician and to the pathologist who is so associated with the clinic that he is able to follow his cases from their first appearance at the clinic to the autopsy, these diseases present widely divergent pictures, making it exceedingly difficult to classify them under a single category.

These difficulties are by no means new. Virchow,¹ for example, spoke of pseudoleukæmia as a "Mischmasch" and stated that the name was selected merely because one did not rightly know how the disease should be regarded and consequently threw into the pseudoleukæmia category everything of this nature which could not be interpreted otherwise. Wunderlich² was of the opinion that in the group of diseases entitled pseudoleukæmia, Hodgkin's disease, and multiple lymphadenoma without leukæmia, *manches nicht identische zusammengebracht ist*.

Our knowledge of Hodgkin's disease has been clarified, or rendered more obscure—depending on the point of view—since Sternberg^{3, 4} demonstrated the close association of the disease with tuberculosis, and from that time on the tubercle bacillus has never been satisfactorily dissociated from the Hodgkin's picture. Von Baumgarten⁵ undertook a classification of tuberculous lymphomata and recognized five subdivisions, namely, granular (Schuppel's), caseous, indurative, fibrocaseous, and lymphogranuloma tuberculosum. Lichtenstein⁶ produced a lymphogranulomatous lesion associated with tuberculosis and tissue reactions of intermediate character in guinea pigs inoculated with material from the spleen of a case of pseudoleukæmic Hodgkin's with tuberculosis. In the later paper⁷ he reviews over 200 of the older contributions on lymphogranulomatosis appearing in the literature previous to 1920.

Since that time, sporadic studies have tended more and more to favor the concept that Hodgkin's disease is a special manifestation of tuberculosis. Vasiliu and Iriminiou⁸ inoculated guinea pigs with material from thirteen cases. In ten of these there was no evidence of an associated tuberculosis yet the material from seven of these ten produced tuberculosis in guinea

pigs. Unfortunately the authors do not state the source of the inocula, *i.e.*, whether from nodes apt to be contaminated secondarily with the tubercle bacillus. Merle⁹ obtained tuberculosis in a single guinea pig inoculated with material from a Hodgkin's node but again does not tell us what node. Bernard, Coste, and Lamy¹⁰ produced tuberculosis in guinea pigs with emulsions of spleen and nodes from Hodgkin's disease. The source of the nodes is not given nor is it stated whether nodes and spleen were inoculated separately or together. The prevalence of tubercle bacilli in certain node groups, especially hilum and, to a lesser extent, cervical and mesenteric, is so well known that conclusions drawn from inoculations from these nodes in Hodgkin's disease must be accepted with some reservations. Coyon and Brun¹¹ report the production of Hodgkin's disease in guinea pigs by inoculation of material from the human subject. The patient likewise had tuberculosis. They are of the opinion that the diseases are unrelated. The source of their material was a mediastinal node. Martinolli¹² inoculated guinea pigs with material from the livers and spleens of foetuses of tuberculous mothers and obtained tuberculosis. Yet in one guinea pig he describes the finding of a typical Sternberg Hodgkin's disease and concludes that the etiological agent of the disease is a filter-passing form of the tubercle bacillus. We must admit that in our own opinion the filter-passing form of the tubercle bacillus still remains to be satisfactorily demonstrated, although the recent studies of Kahn³⁰ on the life cycle of the organism suggest further investigations of this possibility. MacMahon and Parker¹³ have recently cultured human tubercle bacilli from a case showing the conglomerate features of leukæmia, pseudoleukæmia, lymphosarcoma, Hodgkin's disease, and tuberculosis. They wisely refrain from interpreting the picture.

Brandi¹⁴ has recently described an interesting case in which tuberculosis of the testis was followed in six months by Hodgkin's disease in the inguinal nodes. L'Esperance^{15, 17} has obtained tuberculosis in chickens, rabbits, and guinea pigs inoculated with Hodgkin's material and reports the culture of an avian tubercle bacillus from the spleen of a child with typical Pel-Ebstein disease. These results strongly suggest that the avian tubercle bacillus may be the etiological agent in certain cases, at least, of Hodgkin's disease.

During the past year one of the authors has observed a case histologically diagnosed as pseudoleukæmia. This patient was a poultryman who had repeatedly autopsied tuberculous fowls. The initial adenitis which had subsided at the time of admission, was axillary and was associated with a lesion of unknown etiology on the finger. Whereas there was no evidence of classical Sternberg Hodgkin's disease at autopsy and the histological diagnosis was pseudoleukæmia, nevertheless a node removed during the course of the disease showed a distinctly granulomatous picture with many eosinophiles but without definite Sternberg cells. This node was considered as atypical Hodgkin's disease (Case 8, Table IV). A terminal pneumococcal septicæmia was responsible for the death of all animals inoculated with the material. Such cases, in themselves not especially significant, are nevertheless of considerable

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importance when viewed in the light of the gradual accumulation of rather formidable evidence tending to associate Hodgkin's disease with a tuberculous etiology.

Recent studies more directly within the field of known acid-fast etiology appear to have significance, and a possible bearing on the problem under discussion. It is now possible in experimental tuberculosis to estimate the native resistance to initial infection with a given strain of bacilli, and to predict the course of the disease in individual animals, on the basis of the monocyte-lymphocyte ratio as determined from the peripheral blood.¹⁸ Animals showing a high physiological level of monocytes in contrast to lymphocytes are relatively more susceptible to acute, progressive tuberculosis than those having a low M/L index. The epithelioid cell of the tubercle has its origin from the monocyte,¹⁹ and epithelioid cells as identified in the supravital technic have been found as a part of the cellular reaction in Hodgkin's nodes.²⁰

The newer bacteriological studies of Petroff,²¹ based upon an ingenious method for the dissociation of various pure strains of avian, bovine and human tubercle bacilli, are resulting in a reevaluation and a new appreciation of the potentialities for variation in virulence of the acid-fast group. Standard cultures of virulent organisms, long known and studied, have been dissociated through the isolation of individual colonies. The pathology varies widely, depending upon the type of colony picked from a particular strain for inoculation purposes and the state of resistance of the animal, both of these variables now being in a fair way toward control.

Then, the correlated chemical and biological studies of the whole group of acid-fast bacilli under the direction of the Research Committee of the National Tuberculosis Association²² are beginning to suggest new interpretations of the mechanism underlying the varying pathology characteristic of tuberculosis. Among the chemical partitions thus far studied, the phosphatid fraction from the lipoids, as isolated by Dr. R. J. Anderson,²³ of the Sterling Chemistry Laboratory, Yale University, has proven of unusual interest. Given directly into the tissues of normal animals it produces a reaction, predominantly of epithelioid cells and Langhans' giant cells, indistinguishable from that seen frequently in the disease.²⁴ However, when given intravenously in antigenic doses to rabbits the cellular response has been found to be inconstant.²⁵ As small a total dosage of the phosphatid as 5 milligrams may produce small foci of epithelioid cells in organs and tissues, while another rabbit receiving 150 milligrams in larger antigenic doses may show no cellular reaction. In the latter instance an increased ability of the blood serum to flocculate the phosphatid *in vitro* and complement-fixing antibodies^{26, 27} have been demonstrated, together with an increased resistance to subsequent tuberculous infection.¹⁸ When the antibody titre is high, with no free antigen demonstrable, tubercle formation should be minimal; but with lipid antigen being liberated without effective neutralization or elimination by the body,

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TABLE I
Hodgkin's Disease Verified by Biopsy

Case	Age	Sex	Duration mos.	Activity	Treated	Titre	Remarks
1	16	F	8	Active	Yes	H37A3.... 1-320 Av.A3.... 1-640 Anti H37.. 0 Anti Av. \pm 1-20	Fever, rapid extension, death in 4 months
2	51	F	11	Quiescent	Yes	H37A3.... 1-80 Av.A3.... 1-320 Anti A3... 0	No clinical evidence
3	29	M	48	Quiescent	Yes	Av.A3.... 1-640 Bov..... 1-640 H37A3.... 1-2560 Antigens... 0	No clinical evidence
4	34	M	41	Active	Yes	H37A3.... 1-160 Av.A3.... 1-80 Antigens... 0	
5	48	M	7	Active	Yes	H37A3.... 1-640 Av.A3.... 1-640	
6	48	M	36	Quiescent	Yes	H37A3.... 1-640 Av.A3.... 1-640	Active pulmonary tuberculosis
7	22	M	5	Active	Yes	H37A3.... 1-320 Av.A3.... 1-1280	
8	24	F	36	Quiescent	Yes	H37A3.... 1-1280 Av.A3.... 1-1280 Anti H37.. 0 Anti Av... 1-10	Now rapidly progressive
9	45	M	6	Active	Yes	H37A3.... 1-640 Av.A3.... 1-640 (avian heavier)	
10	28	F	50	Active	Yes	H37A3.... 1-640 Av.A3... \pm 1-640	Hæmoptysis; pyelitis; bone involvement
11	29	F	40	Active	Yes	H37A3.... 1-640 Av.A3.... 1-640 Anti H37.. 1-40 Anti Av... 1-40	
12	19	M	27	Active	Yes	H37A3.... 1-640 Av.A3.... 1-320 (avian heavier)	Probably thymic with malignant features
13	21	F	29	Active	Yes	H37A3.... 1-2000 Av.A3.... 1-1000	Progressive; death 8 months later
14	21	F	4	Active	Yes	H37A3.... 1-40 Av.A3.... \pm 640 Av.A3.... 1-320 \pm 1280	Febrile; death in 11 months from onset

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TABLE I (Continued)

Case	Age	Sex	Duration mos.	Activity	Treated	Titre	Remarks
15	27	M	13	Active	Yes	H37A3.... 1-250 ±640 Av.A3.... 1-320	Early recurrent phase after treatment
16	40	M	18	Quiescent	Yes	H37A3.. ±1-40 Av.A3... ±1-40	Anti Av. suggestive; others—o
				Active	Yes	H37A3.... 1-160 Av.A3.... 1-640 Bov..... 1-40	
17	16	M	72	Active	Yes	H37A3.... 1-160 Av.A3.... 1-1280 Anti H37.. ± Anti Av... +++	
18	28	F	36	Active	Yes	H37A3.... 1-160 Av.A3.... 1-640 Antigens... o	
19	40	M	36	Active	Yes	H37A3.... 1-640 Av.A3.... 1-640 Antigens... o	Bone lesions
20	31	M	4	Regressing	Yes	H37A3.... 1-640 Av.A3.... 1-640 Anti H37.. o Anti Av... +	
21	45	F	18	Active	Yes	H37A3.... 1-320 Av.A3.... 1-320 Anti H37.. o Anti Av... +	
22	57	M	3	Active	Yes	H37A3.... 1-160 Av.A3.... 1-320 Antigens... o	
23	22	F	8	Active	Yes	H37A3.... 1-1280 Av.A3.... 1-1280 Bov..... 1-1280 Antigens... o	
24	23	M	5	Regressing	Yes	H37A3.... 1-1280 Av.A3.... 1-640 Bov..... 1-160 Antigens... o	

new foci of epithelioid cells arise, within which the tubercle bacilli appear to survive and multiply with little difficulty.

Comparable phosphatid fractions from human,²⁷ bovine²⁸ and avian tubercle²⁹ bacilli have been isolated by Doctor Anderson and his associates, parallel biological studies having been made by Doctor Sabin and associates at the Rockefeller Institute. It has been determined that this particular lipid fraction, as obtained from all three sources, contains the potentialities for inducing tissue proliferation, primarily epithelioid in character, and may possess anti-

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genic properties. Which of these two reactions, the serological or the foreign body tissue response, will predominate, is dependent upon the constitution of the individual animal.

In testing sera from tuberculous sources of known human or bovine etiology the titre has been higher usually with the homologous antigen, though phosphatid of eterologous origin has been precipitated in relatively high dilution also. Absorption experiments have indicated incomplete precipitation with heterologous, as contrasted with homologous antigens.²⁶ Further chemical and biological studies are in progress to establish whether the phosphatid fractions from human bovine and avian tubercle bacilli are qualitatively, or only quantitatively, different.

In a study during the past two years of more than 350 clinical cases, of which the majority were tuberculous, frequent ability to precipitate the tuber-

TABLE II
Clinical Hodgkin's Disease (No Biopsies)

Case	Age	Sex	Duration	Activity	Treated	Titre	Remarks
1	16	M	17 mo.	Quiescent	Yes	H37A3.... 1-40 ±1-160 Av.A3.... 1-160 Anti H37.. 1-640*	Later suspect this hilum tbc.
2	28	F	36 mo.	Active	Yes	H37A3.... 1-640 ±1-1280 Av.A3.... 1-2000	Terminal phase
3	38	F	4 mo.	Early, regressing	Yes	H37A3.... 1-320 ±1-640 Av.A3.... ±1-2000 (2 hrs) 1-320 (24 hrs) Bov.A3.... 1-320	
4	42	M	23 mo.	Active	Yes	H37A3.... 1-1280 (2 hrs) Av.A3.... 1-640 H37A3.... 1-320 (24 hrs)	Classical course. Dead
5	36	F	5 yrs.	Active	Yes	H37A3.... 1-160 Av.A3.... 1-160	Classical course. Dead
6	28	M	48 mo.	Regressing	Yes	H37A3.... 1-320 Av.A3.... 1-640 Bov..... 1-160	Classical course. Now fever and pruritis
7	22	F	40 mo.	Quiescent	Yes	H37A3.... 1-640 Av.A3.... 1-640 Anti H37.. 0 Anti Av... 1-10	
8	16	M	?	Active	Yes	H37A3.... 1-2560 Av.A3.... 1-2560 Anti H37.. ± Anti Av... ++	

* In this instance a 1-640 dilution of patient's serum against undiluted immune rabbit serum.

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culo-phosphatid in high titre, or the precipitation with a phosphatid antiserum of suspected uncombined antigen, has been demonstrated. Spinal fluids pleural effusions, joint fluids, as well as blood sera have been tested. In a study of tuberculous children and of children vaccinated with Calmette-Guérin bacillus³¹ a reciprocal relationship between the monocyte-lymphocyte ratio and the phosphatid antibody titre in the blood serum has been noted. In tuberculous children when the antibody titre has been low and the M/L index high the patients have been clinically ill, whereas improvement has followed a rise in the antibody titre and an accompanying fall in the M/L ratio.

As a part of the clinical study for an evaluation of this phosphatid precipitin test in diagnosing and following tuberculous infection, we have recorded the reaction of the blood sera from a group of patients at the Memorial Hospital, New York City, showing lymphadenopathies of diverse pathological diagnosis. The cases were seen, the blood serum collected and the precipitin tests read, in the majority of instances, before the results of the biopsy findings and the clinical diagnoses were known. The analysis of the accumulated observations is presented in Tables I to VII inclusive.

Fifty-five cases comprise this series, of which twenty-four fall into the group of Hodgkin's disease as verified by biopsy examination (Table I), and eight additional cases have had a similar clinical diagnosis without histopathological confirmation (Table II). The remaining twenty-three cases

TABLE III
Lymphosarcoma

Case	Age	Sex	Duration	Treated	Active	Titre	Remarks
1	51	M	5 yrs.	Yes	No	H37A3..... 1-80	Verified
2	35	M	5 mos.	Yes	No	H37A3..... 1-40 Av.A3..... 1-40 Antigens... 0	No biopsy
3	50	F	12 mos.	Yes	Yes	H37A3..... 1-40 ±1-80	Verified
4	34	F	5 mos.	Yes	No	H37A3..... 1-40	Mediastinal. No biopsy
5	24	M	12 mos.	Yes	No	H37A3..... 1-320	Tonsillar, primary
6	64	M	2 mos.	Yes	Yes	H37A3..... 1-80 Av.A3..... 1-80 Antigens... 0	Verified. Death in 4 months
7	63	M	6 mos.	Yes	No	H37A3..... 1-640 Av.A3..... 1-160	Verified. No clinical sign of tbc. X-ray neg.
8	51	M	6 wks.	Yes	Yes	H37A3..... 1-40 ±160 Av.A3..... 1-160	Verified
9	48	M	4 mos.	Yes	Yes	H37A3..... 0 Av.A3..... 0	Verified
10	52	F	7 mos.	Yes	Yes	H37A3..... 0 Av.A3..... 0	Verified

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include a variety of pathological conditions involving the lymphatic system, and have been classified partially on biopsy findings, partially on clinical signs and symptoms (Tables III to V; see footnote Table IV).

The difficulty with which activity of the pathological process is measured in a chronic condition such as Hodgkin's disease, together with the influence of intensive irradiation therapy, makes any correlation between the precipitin titre and resistance impossible in this series. Repeated observations on the same case, such as in No. 16, Table I are necessary before any conclusions

TABLE IV
Lymphatic Leukæmia, Pseudoleukæmia, and Leukosarcomatosis (Sternberg)

Case	Type*	Age	Sex	Duration	Activity†	Titre	Remarks
1	Lymphatic leukæmia	55	M	3 mos.	Active	H37A3... 1-80	
2	Lymphatic leukæmia	27	M	4 mos.	Active	H37A3... 1-320 Av.A3... 1-80 Antigens... 0	
3	Lymphatic leukæmia	53	M	14 mos. ?	Active	H37A3... 1-80	
4	Leukosarcomatosis	42	M	9 mos.	Active	H37A3... 1-80 Av.A3... 1-80 Antigens... 0	
5	Leukosarcomatosis	53	M	10 mos.	Active	H37A3... 1-160 Av.A3... 1-160	
6	Pseudo-leukæmia	54	M	?	Active	H37A3... 1-1280 Av.A3... 1-80	
7	Pseudo-leukæmia	50	F	47 mos.	Active	H37A3... 1-160 Av.A3... 1-40 Antigens... 0	
8	Pseudo-leukæmia	36	M	13 mos.	Active	H37A3... 1-320 Av.A3... 1-640 (2 hrs.) 1-160 (24 hrs.)	Node classed atypical Hodgkin's

* To pathologists who realize the changing pictures one encounters in the course of these loosely classified disease conditions it will be quite apparent that it is impossible to group them properly. They change as the disease progresses. As given in the tables the grouping applies to the temporary clinical classification at the time the tests were done.

† Often activity is not determinable. Hodgkin's disease, quiescent so far as external manifestations go, may be active in deep, non-palpable abdominal nodes, bone marrow, etc. No one knows enough about pseudo-leukæmia to say when it is or is not active. We have presumed activity if the blood count varied from the normal. Similar difficulties are presented throughout the whole group of diseases.

are justified. However, the general tendency toward a high antibody titre in this group is consonant with a chronic disease process if interpreted in terms of similar findings in tuberculosis. In nine instances the presence of free phosphatid antigen was suggested in tests with antisera for avian phosphatid, four of the cases giving also a positive precipitin reaction with anti-human tuberculo-phosphatid serum. This observation would lend support to I'Esperance's finding of the avian tubercle bacillus in certain Hodgkin's cases. It is a possibility, of course, that non-tuberculous processes could so alter

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the blood serum that the physico-chemical precipitation of the colloidal suspension of tuberculo-phosphatid would occur. However, it seems less likely that an apparently specific antiserum secured from rabbits, which had been treated with intravenous antigenic doses of this phosphatid, should react with a patient's serum, if a similar antigen was not present. The serum from normal rabbits has not reacted with normal or tuberculous human serum in our experience.

In Table VI are summarized the antibody titres to tuberculo-phosphatid as given under each diagnostic division, and it is here that certain striking differences are to be noted. Twenty-six of the thirty-two cases of Hodgkin's

TABLE V
Heterogeneous Lymphadenopathies

Case	Type	Age	Sex	Duration	Activity	Titre	Remarks
1	Lymphoma	57	F	12 mos.	Quiescent	H37A3... 1-40 Av.A3.... 1-40 Antigens.. 0	Undetermined etiology
2	Chronic lymphadenitis	56	F	24 mos.	Regressing	H37A3... 1-160 Av.A3.... 1-160	
3	Undiagnosed adenopathy	18	F	24 mos. on entry (1925)	Quiescent	H37A3... 1-320 Av.A3.... 1-640	Radiosensitive. May have been Hodgkin's. No evidence in June, 1930
4	Tuberculous adenitis	28	M	5 mos.	Active	H37A3... 1-640 Av.A3.... 1-320	
5	Tuberculous adenitis	28	F	24 mos.	Quiescent	H37A3... 1-40 Av.A3.... 1-40	No evidence of clinical disease when tested

Explanation for abbreviations, Tables I-V.

H37—the H37 strain of human tubercle bacilli.

Av.—avian tubercle bacilli.

Bov.—bovine tubercle bacilli.

A3—Anderson's phosphatid fraction, original concentration 1 per cent. suspension.

Anti H37, anti A3, etc.—reaction between patient's serum and immune rabbit serum prepared by immunizing rabbits against the A3 phosphatid.

disease showed a capacity of the blood serum to precipitate the phosphatid in a dilution of 1-640 (of an original 1 per cent. suspension), or higher. This is well within the range of positive reactions observed in known tuberculous cases. Only three of the twenty-three cases, which were not of the Hodgkin's type, showed a similar precipitating ability, and one of these was an active case of tuberculous adenitis (Case 4, Table V), and another an undiagnosed adenopathy suggestive of Hodgkin's disease (Case 3, Table V). Two of the cases in the miscellaneous group, which were diagnosed clinically, when first seen, as Hodgkin's disease, were reported with low, 1-40, 1-80, precipitin titres previous to the biopsy diagnosis of lymphosarcoma. The coincidence, if such it be, between a high anti-phosphatid titre in the serum and

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the presence of Hodgkin's disease has been sufficiently frequent in this series to raise the question of the correctness of this diagnosis in the adenopathy group, when the precipitin reaction has been negative, or positive only in the non-specific range. With reference to an etiological relationship between the tubercle bacillus and Hodgkin's disease we are not unmindful of the frequency with which true tuberculous disease has been found associated with the typical pathological picture of Hodgkin's and the suggestive results of these tests may hardly more than emphasize this long-recognized relationship.

TABLE VI
Analysis of Results with Tuberculo-phosphatid

Type of disease	Titres				
	160 or above	320 or above	640 or above	1280 or above	2000 or above
Verified Hodgkin's.....	24 of 24	23 of 24	20 of 24	8 of 24	2 of 24
Clinical Hodgkin's—no biopsy.....	8 of 8	6 of 8	6 of 8	4 of 8	3 of 8
Lymphosarcoma.....	2 of 8	2 of 8	1 of 8	0	0
Pseudoleukæmia.....	3 of 3	2 of 3	2 of 3	1 of 3	0
Lymphatic leukæmia....	0	1 of 3	0	0	0
Leukosarcomatosis.....	1 of 2	0	0	0	0

It will be seen from Table VII that in less than half of the cases of Hodgkin's disease was the titre for avian phosphatid higher than that for the human lipid, though in nineteen of the twenty-four verified cases the avian titre was equal to, if not above, that of the human. Biologically the phosphatids from both sources produce an identical reaction of epithelioid cells in the connective tissues of normal rabbits, and no qualitative differences have as yet become apparent in the experimental studies.

TABLE VII
Specificity of Antigens

Type of disease	Avian titre higher	Avian equals human	Human titre higher
Verified Hodgkin's.....	10 of 24	9 of 24	5 of 24
Hodgkin's unverified.....	4 of 8	3 of 8	1 of 8
Pseudoleukæmia.....	1 of 3		2 of 3

Hodgkin's disease is comprised of several heterogeneous but interlocking pathological manifestations. It may be an ill-defined chronic lymphadenitis with slight to moderate reticulum cell overgrowth, or proliferation of the sinus endothelium, and a slight eosinophilic infiltration, or it may present as a more or less diffuse overgrowth of small lymphocytes associated with a low-grade pseudoleukæmic blood picture; but, in the fully developed, typical types, there is the characteristic Sternberg cell histology, and on occasion a tendency toward various sarcomatoid manifestations. When studied supravitaly,²⁰ nodes from cases seen early in the disease show many epithelioid cells entirely

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characteristic of those found in tuberculosis. In the later stages of the disease there are perhaps fewer epithelioid cells and a more general connective tissue reaction. Differences between these pictures and classical caseous tuberculosis are striking only when the extremes are considered. There are many examples which reveal interrelationships, and cases in which it is quite impossible to determine where one type ends and the other begins. Hodgkin's disease differs from typical tuberculosis hardly more than the various manifestations of clearly recognized tuberculosis differ from one another—no more than pleurisy with effusion differs from phlyctenule, or hyperplastic tuberculosis of the cæcum from acute pneumonic phthisis or lupus erythematosus.

That Hodgkin's disease pursues an inevitably fatal course is scarcely a sound argument against a tuberculous etiology. In the first place, it is never treated as is tuberculosis; secondly, involvement is usually extensive when patients are first seen; and in the third place, it is impossible to estimate the number of transient lymphadenopathies never subjected to microscopic diagnosis, which if so studied, might show features which would necessitate the diagnosis of Hodgkin's disease. We, personally, have known one patient (biopsy verification), who survived gland excision seventeen years, and who now has a local recurrence of the process with some dissemination, but who gives promise of surviving many years longer.

With the newer histo-pathological approach to the finer cellular differentiation and structure in disease processes, which is now possible through the use of supravital staining with its additional criteria, we may hope eventually to understand more fully the meaning of these reactions of diverse etiology in terms of physiological equilibria and resistance. The body has at its disposal only a limited number of cells with which to combat invasion and insult from whatever source, and this is the underlying reason for the confusion which attends the attempt at differentiation in such a closely allied group of diseases as those affecting the lymphatic system.

The recent work of Petroff³² on the bacteriology of the acid-fast bacilli necessitates a restudy of this group of organisms in their relationship to human disease. A careful comparative study of the protein antigens (allergy and skin hypersensitiveness) from the several "R" and "S" strains of tubercle bacilli is now essential, and quite possible. The differing pathology, which has already been found to accompany the various combinations of constitutional resistance and these diverse types of infecting organisms, presents a fertile field for present speculation and future investigation.

An ultimate understanding of both the pathological agent or factor, and the mechanism of adjustment or resistance must precede any final approach toward the control of each definite etiological entity in disease.

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THE GENETIC NEOPLASTIC RELATIONSHIPS OF HODGKIN'S DISEASE, ALEUKÆMIC AND LEUKÆMIC LYMPHOBLASTOMA, AND MYCOSIS FUNGOIDES

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IN 100,000 diagnostic tissue examinations made in the Pathological Laboratory of the University of Michigan between the years 1895 and 1927 there were 506 cases, approximately 0.5+ per cent. of all cases, diagnosed as Hodgkin's disease, aleukæmic and leukæmic lymphoblastoma, and mycosis fungoides. These cases were further distributed, as to diagnosis, as follows:

Hodgkin's

Typical Hodgkin's	94
Atypical Hodgkin's	83
Sarcomatous Hodgkin's	29
Leukæmic Hodgkin's, lymphatic	6
Leukæmic Hodgkin's, myelæmic	2
Hodgkin's becoming lymphosarcoma	12
Abdominal Hodgkin's	3
Hepatic Hodgkin's, cirrhosis	2
Cutaneous Hodgkin's, mycosis	1
(Non-caseating tuberculosis with clinical diagnosis of Hodgkin's	10)

Lymphoblastoma (lymphosarcoma)

Typical glandular lymphoblastoma	134
Typical abdominal lymphoblastoma, gastro-intestinal, etc.	26
Typical tonsillar lymphoblastoma	19
Typical aleukæmic lymphoblastoma becoming leukæmic	9
Atypical glandular lymphoblastoma	44

Mycosis fungoides

Aleukæmic lymphoblastoma	23
Aleukæmic lymphoblastoma becoming leukæmic	5
Aleukæmic myeloblastoma	1
Leukæmia cutis	3

During the same period, in 2,000 autopsies there were 83 (4.1 per cent.) cases falling into the same diagnostic categories, as follows:

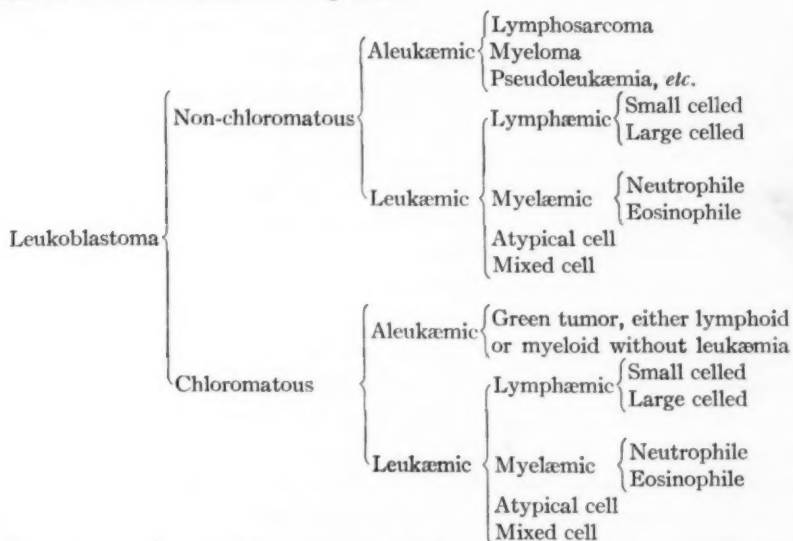
Myelæmic leukæmia	24
Leukæmic lymphoblastoma	20
Aleukæmic lymphoblastoma	20
Hodgkin's, typical	7
Aleukæmic mycosis fungoides	5
Leukæmic mycosis fungoides	3
Hodgkin's mycosis fungoides	1
Plasma-celled mycosis fungoides	1
Myeloid mycosis fungoides	1
Eosinophile (myelocyte) mycosis fungoides	1

The study of this material, as outlined above, has formed the basis for the writer's belief that Hodgkin's disease is a neoplasm and related genetically to the lymphoblastomas, of which both the aleukæmic and the leukæmic forms are identical pathologically; and that mycosis fungoides is likewise a neoplasm belonging to the same generic group. The essential differences between these different clinical forms consist in different degrees of differentiation or entdifferentiation, and the organ or tissue primarily involved. Transition forms exist between all of these groups, and one type may be transformed into another. Clinically they all possess the characters of malignancy; no cure is known for any one of them; they progress inevitably to a fatal termination, sometimes rapidly, sometimes very slowly. They all show infiltrative tendencies and metastasize, ultimately involving all of the reticulo-endothelial and blood-cell forming tissues of the body. They show an abundance of mitotic cell-division figures, both typical and atypical, as well as amitotic cell division. Their growth is at times rapid, at other times slow; they are characterized by their marked tendency to degenerations and necrosis. Marked fibrosis often follows the degenerative changes. At times the regressive tendencies are so marked that so great a reduction in size of the growths takes place, that clinically they may become so greatly diminished in size as apparently to disappear. A certain degree of fever frequently accompanies such periods of marked retrogression. Periods of the aleukæmic state may alternate with leukæmic periods. The acute transformation into a leukæmia is sometimes preagonal. The general effects upon the patient are in every way comparable to those of tumor cachexia; progressive anæmia, emaciation, weakness and exhaustion. Although regarded many times as representing infectious processes, no organism described as a possible etiologic factor has ever met the test; moreover, the clinical and pathologic pictures presented are those of a progressive fatal malignancy. No mild cases exist; no cures have ever been observed for any one of the forms belonging to this group. There is no evidence of any immunity process; no specific antibodies are found in the serum. In all of these forms the pathologic picture is that of a progressive increase of atypical tissue replacing the normal tissues of the body, up to a point at which life is no longer possible, or secondary complications may end the picture.

More than twenty-five years ago the writer's study of chloroma convinced him that "Chloroma is a tumor-like hyperplasia of the parent-cells of the leucocytes, primary in the red marrow, the periosteum being involved only secondarily." This was new pathology at the time, but this view has been generally accepted since. In 1904 he observed an aleukæmic lymphosarcoma (lymphoblastoma), primary in the intestine, become transformed into the leukæmic stage after a surgical operation for removal of the appendix. This case was reported in the *Transactions* of the Association of American Physicians, in 1904, under the title of "The Neoplasm Theory of Leukemia, with Report of a Case Supporting This View." It was regarded by the writer as presenting the same evidence of malignant neoplasm nature, in its infiltrations and metastases, as did the chloroma case, and in this article he

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made the statement that "leukemia must be regarded as a neoplastic hyperplasia of the parent cells of the blood cells." For this neoplasm, he suggested the term *leukoblastoma*, and offered the following classification of the leukæmic and aleukæmic neoplasms:



This was at a time when no textbook considered the possibility of the neoplastic nature of leukaemia, but a certainty of conviction as to the correctness of this view has remained in the writer's mind ever since, and he has had in recent years the satisfaction of seeing an increasing acceptance of this view. In spite of the prevailing universal belief that Hodgkin's disease was an infective granuloma, he very early was led to include this disease in the same group with the aleukæmic and leukæmic lymphosarcomas, because of observed cases showing such transitions from typical Hodgkin's into the other forms. His experience was the same as far as mycosis fungoides was concerned, and this clinical form he brought also into the same group of generic relationship. While the limits of this paper are too brief to enter into any detailed description of epoch-making cases observed, or into extended arguments over the relationship of the different forms, an attempt will be made to give a concise and succinct statement of the writer's views on this question, and the chief reasons in support of these views.

Hodgkin's Disease.—Typical Hodgkin's presents a characteristic and easily recognizable histological picture. The most marked feature is at first a localized or focal proliferation of the reticulum with the presence of atypical lymphocytes, lymphoblasts, plasma cells, mononuclear and polynuclear eosinophiles, myeloid cells, fibroblastic cells, and the multinucleated "Hodgkin's" or "Dorothy Reed" giant cell, which resembles those of the bone-marrow. These and the eosinophile cells constitute the chief diagnostic factors microscopically; and our diagnoses of typical Hodgkin's rests upon their presence and is never made in their absence. As the disease becomes more chronic these foci in these lymph-nodes become more fibrous, the struc-

ture of the node is wholly lost, and its appearance becomes that of a multicentric nodular mass, the active nodules separated from each other by dense fibrous connective tissue. In the more actively growing cellular forms degeneration and necrosis occur frequently; often these degenerative changes are so marked that a great reduction in their size, even to that of the normal node, may result. The disease may begin anywhere in the body where there is primitive lymphoid tissue or reticulo-endothelial tissue. In our experience the left cervical nodes have been most often the clinical point of origin; then the right cervical region; then the axillary, inguinal, mediastinal, and retroperitoneal nodes in the order named. The process may also be primary, or at least most marked, in the tonsil, thymus, bone-marrow, spleen, liver and skin. We have diagnosed Hodgkin's in the tonsil before any enlargement of the lymph-nodes was clinically apparent. Ultimately, all of the lymphoid tissue in the body is involved in the process, and throughout the reticulo-endothelial tissues of the peri-lymph-node adipose tissue, in the mediastinum, retroperitoneal adipose tissue, and subcutaneous fat, small nodules, or more diffuse infiltrations, showing the same histologic structure as the lymph-nodes develop. Even in the meninges Hodgkin's foci may be present. In old and advanced cases the liver may present the appearance of a Hodgkin's cirrhosis; even in the kidneys and testes metastatic nodules and infiltrations may be found. The lungs may also not infrequently show numerous typical Hodgkin's nodules and infiltrations. The heart usually escapes, but even in this organ we have found small Hodgkin's nodules, and in one case of mediastinal Hodgkin's (thymoma) the heart showed marked involvement. Further, in late Hodgkin's atypical cells are found in small masses in the splenic, kidney and liver capillaries, apparently free, or forming small emboli, proving beyond any doubt the occurrence of metastasis. When recognized clinically the disease is as a rule well advanced and the majority of the lymph-nodes show the typical lesion. As the lymph-nodes become progressively replaced by the atypical tissues, all normal lymph-node structure disappears, the sinuses are obliterated, the germ centres are lost, and the distinction between cortex and medulla can no longer be made out. Around the nodes so altered there is a progressive new formation of lymphoid tissue which in turn becomes involved in the process. After removal of diseased nodes there occurs a similar regeneration of nodes that ultimately show the characteristic changes of the disease. Not all cases of Hodgkin's show a febrile reaction, but in the majority there is an irregular fever curve, especially marked in the case of degenerating nodes. Secondary infection of the necrotic areas is undoubtedly responsible for the septic fever curves and night sweats found in some cases. The disease occurs most frequently in the young adult; our earliest case was in a child three years old, and the oldest in a male of seventy. It is relatively uncommon after the age of forty. The usual limit of life after relatively early diagnosis is three to five years. X-ray irradiation is the only treatment that will prolong life; in some cases under constant and experienced supervision the limit of life has been extended to seven, nine, ten and twelve years. In spite of repeated irradiation the disease process ultimately conquers, and in

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these late cases there is an extraordinary extension of the lesions to practically all organs and tissues. In two of our X-ray cases there occurred a transformation of the pathological lesions into those of myelæmic leukæmia; in six other cases lymphatic leukæmia developed spontaneously without X-ray irradiation. There were three primary abdominal Hodgkin's in this series, involving particularly the spleen, a splenomegaly being the chief clinical feature; and the disease was diagnosed in this organ after splenectomy, which was followed by a gradual generalization of the process. In two cases the chief clinical symptoms were hepatic, and microscopic examination of the enormously enlarged livers showed typical Hodgkin's involvement of all the periportal tissues—a pathological picture justifying the use of the descriptive term, Hodgkin's cirrhosis. The spleen showed similar lesions in these cases, and Hodgkin's foci were found in the lymph-nodes and bone-marrow, but nowhere to the extent shown in the liver. Further, in one clinical case of mycosis fungoides the skin lesions were typically those of Hodgkin's. In ten cases diagnosed clinically as Hodgkin's, a diffuse miliary non-caseating tuberculosis was found in the excised nodes. One of these cases treated twenty-five years ago with old tuberculin recovered and is still alive.

As atypical Hodgkin's we designate cases in which the atypical myeloid cells, "Dorothy Reed" cells and eosinophiles are either few in number or absent. The focal or nodular replacement of the lymph-nodes by fibrous connective tissue, or atypical lymphoid tissue, with all of the clinical picture of Hodgkin's, constituted the basis for the diagnosis of Hodgkin's and clinical observation confirmed this in the majority of these cases. Of a few cases in which biopsies were secured months or years later, some showed typical Hodgkin's lesions, others the microscopic picture of lymphosarcoma or reticulocytosarcoma; for the greater part this group represents transition forms to the sarcomatous type of lesion, and we would today place them in this category.

By sarcomatous Hodgkin's we mean very actively growing, diffusely cellular rather than nodular lesions, with few or no eosinophiles or Dorothy Reed cells, and a greater tendency to infiltrate and to metastasize, particularly in the kidneys and lungs. The sarcomatous transformation of a Hodgkin's may proceed in one of two directions, either leading to a lymphosarcoma or to a large-celled form, with abundant reticulum and numerous giant cells, which we have styled a reticulocytoma or reticulo-endothelioblastoma. The former arises through the overproduction of maternal lymphoblasts, the resulting growths being typical lymphoblastomas (lymphosarcomas), either small celled or large celled. All lymph-node structure is lost, the germ centres and sinuses disappear, cortex and medulla become converted into a uniform mass of atypical lymphocytes with many large maternal lymphoblasts scattered throughout, and there is an infiltration of the capsule and pericapsular tissues. Ultimately, in place of the Hodgkin's lesion all of the lymphoid tissues of the body assume the character of the lymphoblastoma. In twelve of our cases repeated biopsies showed the progress of this transformation from a typical Hodgkin's to a typical lymphoblastoma, with com-

plete absence of eosinophiles, giant cells, myeloid cells, and disappearance of the reticulum. Usually the resulting lymphoblastoma is aleukæmic, but in six of our cases there gradually developed the blood picture of a lymphatic leukæmia. In the reticulo-endothelioblastoma form, the lymphoid cells become reduced in number, the eosinophiles disappear, and the majority of the cells come to be large polymorphic cells with abundant cytoplasm, and possessing many large hyperchromatic nuclei. Numerous giant cells of the myeloid type occur, and the appearances may be those of a large round-cell sarcoma of malignant type. The reticulum is usually very abundant and prominent, forming an interlacing network of coarse fibrils in the spaces of which lie the sarcoma cells. This form shows a greater degree of malignancy than either the type Hodgkin's or the lymphoblastoma. It is especially likely to develop metastases in the kidneys, and the spleen is involved earlier than in the other two forms. In some cases a rapid enlargement of the liver results

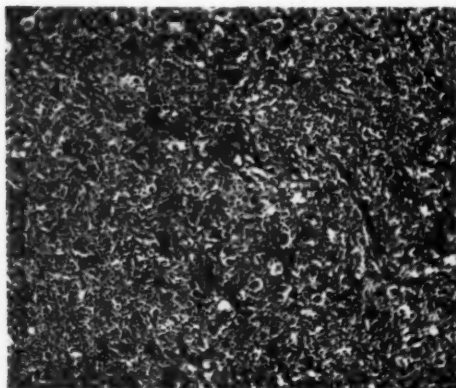


FIG. 1.—Transformation of a Hodgkin's into a reticulocysto-endothelioblastoma. Ultimately all traces of the Hodgkin's lesion disappeared.

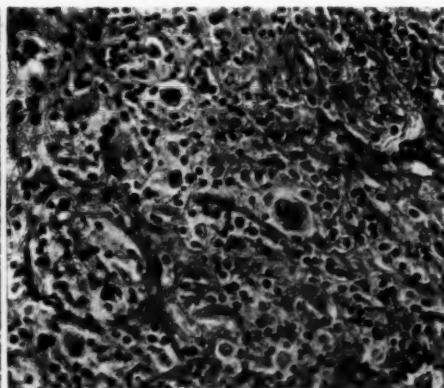


FIG. 2.—Sarcomatous Hodgkin's. Transformation into reticulocysto-endothelioblastoma.

from the marked infiltrations of the periportal tissues. In our material there were twenty-nine cases of this type of sarcomatous Hodgkin's, and in a number of these the process has been followed in successive biopsies extending over a number of years, in one case over seven years (controlled by X-ray irradiation). We have seen one case of this type proceed to a rapidly fatal termination in a child just over one year of age, the lesions presenting from the beginning the histologic picture of the reticulo-endothelioblastoma. Without irradiation the clinical course of this type is usually more malignant and shorter. Finally, in irradiated cases of Hodgkin's, after some years, the Hodgkin's lesion may be replaced by the sarcomatous, and the case be brought to a speedy termination. In the one case of Hodgkin's mycosis fungoides seen by us, typical Hodgkin's lesions were found in the cutaneous growth and in the lymph-nodes. The clinical history of this case was characteristic of mycosis fungoides, with a ten-year pre-mycotic stage of skin lesions before the development of the fungating growths.

Lymphoblastoma (Lymphosarcoma).—In one hundred and thirty-four cases of biopsies from enlarged lymph-glands microscopic examination showed

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the presence of typical lymphoblastoma. In the majority of these the left cervical region was primarily involved, or showed a more advanced stage of the disease. In twenty-six cases the growths were apparently primary in the gastro-intestinal tract. Nineteen cases were diagnosed in the routine examination of tonsils, and later showed enlargement of the cervical nodes. One of these cases lived for seventeen years after the diagnosis had been made upon his enlarged tonsil, dying ultimately of generalized lymphoblastoma. Another case lived for thirteen years after the tonsil diagnosis, dying with generalized lymph-node enlargement. In both of these cases the extension of life was undoubtedly due to the systematic use of X-ray irradiation. Microscopically, all of these cases presented the same histologic picture, an atypical diffuse lymphoid hyperplasia (usually small celled) with loss of germ centres and normal architecture, and with infiltrations extending beyond the capsule of the node. The majority of these growths were medullary and

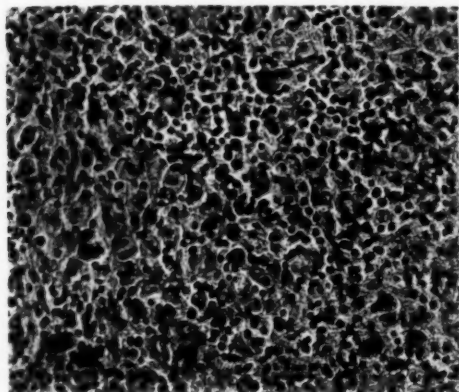


FIG. 3.—Sarcomatous Hodgkin's. Transformation into lymphoblastoma.

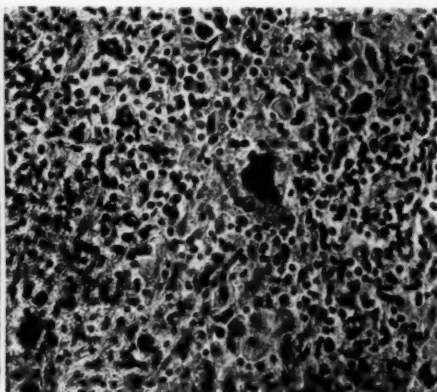


FIG. 4.—Transformation of a Hodgkin's to a lymphoblastoma. Traces of Hodgkin's foci still persistent.

showed but little stroma; in only a few was there an abundant stroma. In the latter the cells were often of the type of large lymphocytes, rather than of the small lymphocyte. The majority of these cases of lymphoblastoma showed clinically more or less febrile reaction, resembling that in the Hodgkin's cases. Similar degenerative changes (necrosis) occurred also in the enlarged nodes. Nine cases showed a transformation from the aleukæmic stage to the leukæmic. In the twenty autopsy cases of lymphatic leukæmia practically the same glandular lesions were found as in the twenty autopsy cases of aleukæmic lymphoblastoma. In both forms the kidneys usually presented large and numerous metastases, the liver showed marked lymphoblastomatous infiltrations of the periportal tissues, and the spleen showed a diffuse lymphoblastomatous metaplasia. Infiltration in the retroperitoneal adipose tissue and in the lungs also was frequent. In several cases of the large-celled form coming to autopsy emboli of large atypical cells were found in great numbers in the pulmonary, liver, splenic and renal vessels. In forty-four of the biopsy cases a diagnosis of atypical lymphoblastoma was rendered

because of combined features of Hodgkin's and lymphoblastoma, or of reticulo-endothelioblastoma and lymphoblastomatous hyperplasia. In our experience the response to X-ray irradiation of the aleukæmic form of lymphoblastoma has been on the whole much better than in the case of Hodgkin's, but even after several years of apparent disappearance of the enlarged nodes recurrence takes place with a fatal ending.

Mycosis Fungoides.—In the great majority of cases this disease is a small-celled lymphoblastoma involving the primitive lymph-nodes of the papillary layer of the dermis, but ultimately coalescing to form the fungoid tumors of the skin, becoming generalized at last in all of the lymphoid tissues of the body, lymph-nodes, spleen, bone-marrow and thymus, and presenting the same periportal infiltrations in the liver, and renal metastases that are characteristic of primary lymphoblastoma of the regional lymph-nodes. It also may become leukæmic, or may be associated with a leukæmia from the beginning

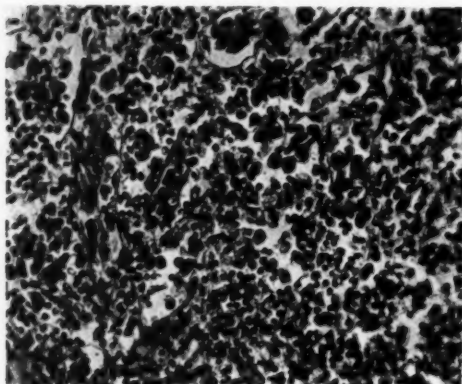


FIG. 5.—Lymphoblastomatous transformation of Hodgkin's. Biopsy two years previously showed typical Hodgkin's. Present biopsy showed complete disappearance of Hodgkin's lesion, with replacement by lymphoblastoma. Confirmed by further biopsies.

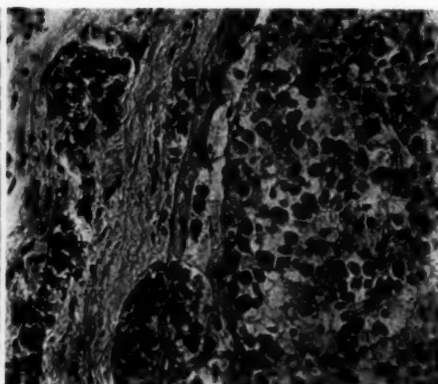


FIG. 6.—Lymphoblastomatous transformation of Hodgkin's disease. Infiltration of neoplastic process through capsular blood-vessels.

(leukæmia cutis). In one of our cases coming to autopsy the infiltrations in the skin were typically those of Hodgkin's disease; in another the cells were chiefly of the plasma-cell type; in another they were myeloid in character, while in another case the infiltrations and the skin tumors consisted chiefly of eosinophile cells, mostly mononuclears. Aside from the skin involvement, which may precede or follow that of the regional lymph-nodes, the pathologic picture is that of a generalized lymphoblastoma. When primary in the primitive lymph-nodes of the skin the development of the disease may be very slow; a "pre-mycotic stage" of several years' duration may precede the development of actual tumors in the skin. In our material there were twenty-three cases of the aleukæmic form of lymphoblastoma, and five cases showing a transformation from the aleukæmic to the leukæmic stage, while three cases were of the leukæmic cutis type from the beginning of the process. Other observers have noted the occurrence of the Hodgkin's type of lesion in the cutis, but the writer has found no reported case of the eosinophilic form. It is possible that some of the cases diagnosed clinically

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as multiple hæmorrhagic sarcoma of Kaposi may be related to mycosis fungoides. In our material we have had but one biopsy from such a case, and the microscopic picture appeared indistinguishable from that of the early pre-mycotic stage of mycosis.

The above brief analysis of our material forms the foundation upon which the following conclusions are drawn:

1. Hodgkin's disease, sarcomatous Hodgkin's, aleukæmic and leukæmic lymphoblastoma, aleukæmic and leukæmic mycosis fungoides are all true neoplasms and are genetically closely related.

2. Transition forms between all of the types exist.

3. They differ chiefly in the degree of entdifferntiation shown by their cell types, and in their point of origin.

4. They all take their origin from perivascular reticulo-endothelium, or the maternal lymphoblasts of the lymphoid tissues of the body.

5. Those arising from the hæmatopoietic perivascular reticulo-endothelium take on the type of Hodgkin's, sarcomatous Hodgkin's (reticulocyto-endothelioblastoma), or even of myeloid forms of sarcoma. Those arising from the maternal lymphoblasts have the character of the lymphoblastoma, small-celled or large-celled, aleukæmic or leukæmic. The maternal lymphoblasts are derived from the same perivascular reticulo-endothelium, but represent a higher stage of differentiation than do the Hodgkin's and the reticulocyto-endothelioblastoma forms. The sarcomatous Hodgkin's of the reticulocyto-endothelioblastoma type represents a greater entdifferntiation than the Hodgkin's type; while the lymphoblastoma represents a higher stage of differentiation.

6. The more undifferentiated forms, Hodgkin's, sarcomatous Hodgkin's and typical lymphoblastoma forms occur chiefly in individuals of younger ages; while the typical aleukæmic and leukæmic neoplasms are more frequent in older individuals.

7. They all run a similar clinical course, often with fever, characterized by remissions and recurrence of the tumors, with the development of a progressive tumor cachexia, anæmia, emaciation and prostration. No case has ever been cured; when removed surgically the regenerated glands become similarly involved in the process. While suggesting analogies with chronic infectious processes, they differ from these in that no mild or cured cases occur, there is no evidence of any immune reaction on the part of the organism, and the process shows a steady malignant progression to the fatal termination.

8. Pathologically, the lesions are neoplastic in type, rather than granulomatous; they show true infiltrations and metastases. In their cell types and architecture they follow definite patterns which cannot be explained on the basis of an inflammatory reaction.

9. There is but one method of treatment, which will delay, but will not halt, the inevitable malignant progress of these growths, and that is the judicious and systematic employment of X-ray irradiation.

STUDIES IN HODGKIN'S DISEASE

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THE idea of the tuberculous nature of Hodgkin's disease has never really been lost sight of by the students of that disease since it was first expressed by Sternberg in 1899. Ewing has always emphasized the close relationship between Hodgkin's disease and tuberculosis, which is indicated by the very similar granulomatous nature of the two processes, by the frequent finding of acid-fast bacilli in the lesions, by the rarely positive atypical reaction produced in experimental animals, and by the frequent incidence of generalized tuberculosis as a terminal manifestation in this disease. Furthermore, he points out that "tuberculosis follows Hodgkin's disease like a shadow." Subsequent to the investigation of Much, Ewing identified Gram-positive granules, and occasionally acid-fast rods in many of the lesions of Hodgkin's disease, which further strengthened his theory that the tubercle bacillus plays an important part in the etiology of this disease.

As has just been stated, the granulomatous character of the typical lesions spoke strongly in favor of this conception and the finding of the characteristic granules by Much in 1910, and the recent studies by Kahn have revived it. A strong argument in favor of this opinion was the fact that the majority of guinea-pig inoculations with Hodgkin's lesions resulted negatively with respect to tuberculosis. In other words, the tubercle bacilli that have been demonstrated in Hodgkin's nodes appear to have represented an independent infection. Therefore, it seemed to me that if Hodgkin's disease is tuberculous, and is not caused by the human or bovine variety, as evidenced by the negative animal experiments, the disease might be due to the hitherto completely ignored avian tubercle bacillus.

In the experimental animal inoculations previously reported, only guinea pigs, rabbits and monkeys had been used; that is, animals relatively -insusceptible, or immune, to avian infection. As the guinea pig was the animal most frequently employed in the reported cases of experimental inoculation with Hodgkin's material, it was determined to carry on a series of preliminary experiments to test the resistance of this animal to avian infection, and to find out whether an increased susceptibility could be produced by the previous inoculation of heterologous strains of tubercle bacilli.

For this purpose one series of animals was inoculated with live avian tubercle bacilli. A second series was treated with killed human tubercle bacilli before inoculation with the live avian organisms, and a third group received killed bovine bacilli as a preliminary injection before inoculation with the live avian bacilli.

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It was found, as the result of these experiments, that guinea pigs have a natural resistance to avian infection, shown by the long period of incubation, six to eighteen months, before generalization of the disease. The lesions developed also differed from those usually seen in animals inoculated with human tuberculosis, in that they seemed to have a predilection for the lymphatic system, shown by the extensive involvement of all nodes; cervical, axillary, mediastinal and bronchial, with less significant, although sometimes extensive, lesions in the liver, lungs and spleen.

The nodes, on microscopic examination, revealed the characteristic Sternberg-Reed histology.

These observations seemed to establish the fact that guinea pigs, although relatively insusceptible to avian infection, nevertheless occasionally develop a delayed and atypical tuberculosis and suggest that the preliminary inoculation of guinea pigs with killed human bacilli renders them less resistant to avian infection.

Furthermore, these findings offer an explanation for the negative or delayed positive inoculations obtained in the reported experimental inoculations of guinea pigs with Hodgkin's lesions. They also answer a strong objection to my thesis, which I encountered early in my study, namely, that the avian tubercle bacillus is not pathogenic for mammals.

On the strength of these results, I concluded that the simplest way to determine whether Hodgkin's disease was at all related to the avian tubercle bacillus, was to inoculate birds with Hodgkin's lesions, an experiment which, so far as could be ascertained, had never been reported.

Therefore, in November, 1926, I undertook a series of experiments on chickens to test this theory.

Five healthy chickens were inoculated intravenously with emulsions of lymph-nodes from two cases of clinically and histologically characteristic Hodgkin's disease.

All of these chickens developed either a typical or an atypical tuberculosis, and in the tissue smears, stained by Ziehl-Nielsen method, acid-fast granules and rods, extra- and intracellular, were demonstrated in two of them, and non-acid-fast granules in another.

Re-inoculation of material from the lesions of one of these chickens into another chicken produced an identical, though more extensive, manifestation of the disease.

An atypical tuberculosis developed in guinea pigs after inoculation of the tissue from the fourth chicken. A growth of bacteria with the staining and cultural characteristics of the avian tubercle bacillus was produced on egg media from material from this guinea pig.

Cultures from these birds on egg media were contaminated in all instances. In one the chicken culture gave a symbiotic growth of a blastomyces-like organism with an acid-fast bacillus.

While it was recognized that the two short series of experiments here reported could not quite exclude the apparently unlikely alternative explana-

tion that we were dealing with an accidental avian infection, the findings seemed to justify the conclusion that in these chickens, a lesion with the histological features of Hodgkin's granuloma and comparable to avian tuberculosis had been produced after the inoculation of emulsified Hodgkin's nodes. This might indicate that the etiological agent in certain forms of Hodgkin's disease is pathogenic for birds, or that the *avian tubercle bacillus* is a factor in producing some of the lesions which are interpreted as Hodgkin's disease.

This evidence could not be considered conclusive on account of the small number of experiments, and the lack of *pure culture* of that organism from the inoculated birds. However, since that time I have studied four other cases, which confirm the previous findings and include the successful isolation of an acid-fast bacillus possessing some of the cultural characteristic of the avian tubercle bacillus. One of these cases, submitted to me from the Memorial Hospital, was the rather rare form of Hodgkin's granuloma, known as Pel Ebstein's disease, in which the gradual splenic enlargement with intermittent attacks of fever are the most prominent features, the associated lymph-node involvement being either absent or insignificant.

The histological study suggested the presence, mainly in the spleen, of an atypical Hodgkin's disease, the lesions consisting almost entirely of focal necrosis. Direct smears from spleen stained by Ziehl-Nielsen's method showed a few acid-fast bacilli, and cultures on egg media gave a scant growth resembling the avian type of tubercle bacillus. The fresh macerated splenic tissue was inoculated into four chickens, one rabbit intravenously, one rabbit subcutaneously, and also into four guinea pigs, two of which were previously treated and two normal ones. One of the chickens was accidentally killed four months after injection. The other three lived from six to twelve months. All of these birds, at autopsy, showed lesions of avian tuberculosis in liver and spleen, with typical Sternberg-Reed histology. Acid-fast organisms were found in direct smears and in stained sections. Cultures on egg media from the liver and spleen of these chickens showed a growth similar to that obtained from the original splenic material; the rabbit inoculated intravenously died of acute septicæmia twenty days after injection; and cultures on egg media gave a growth with the characteristics of the avian tubercle bacillus. Re-inoculation intravenously into a second rabbit produced similar lesions, and positive cultures of tubercle bacilli were recovered.

The rabbit inoculated subcutaneously lived six months and the autopsy revealed typical generalized tuberculosis.

Of the four guinea pigs injected, the two previously treated with killed human tubercle bacilli died about eleven months after injection, with extensive lymph-node tuberculosis. The other guinea pigs are still alive, twenty-two months after inoculation.

The findings in this case seem to be of value in offering evidence of the avian tuberculous nature of a condition which presents a histological relationship to typical Hodgkin's disease and indicates that in the human being,

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as well as in the lower animal, avian infection may be exhibited in various pathological lesions.

Another case was one of Hodgkin's disease in a child of eight years, in which the prominent symptoms were generalized involvement of cervical mediastinal bronchial and retroperitoneal lymph-nodes with enlargement of the spleen.

Biopsy of the nodes showed the typical histology of Hodgkin's disease, and this histological diagnosis was confirmed at autopsy.

Emulsified material from these nodes was inoculated into two treated guinea pigs, intravenously into two normal chickens and one rabbit subcutaneously. All of these experimental animals, except the rabbit, developed tuberculosis, and positive tubercle cultures on egg media were obtained from the lesion.

This study permits the conclusion that Hodgkin's disease may represent an atypical tuberculosis, possibly avian in type.

A recent case may be added to this group:

A young man of twenty-seven years had had his tonsils and right cervical lymph-nodes removed in 1920, and enlarged cervical and axillary nodes removed in 1927. At both of these operations the histologic diagnosis was tuberculosis and the patient's recovery prompt. Four months before his death he had a chill, following exposure, and developed pneumonia. He recovered in three weeks, but after this had a persistent afternoon temperature, usually between 100 and 101 degrees. When admitted to the hospital, he had enlarged lymph-nodes in both sides of the neck, and the X-ray diagnosis was consistent with the autopsy findings. The sputum was negative for tubercle bacilli on ten occasions.

The post-mortem examination revealed massive lymphoma of thoracic and abdominal lymph-nodes with extension into the liver and spleen. These lesions were associated with hydrothorax, hydropericardium, ascites, and recent acute endocarditis. The latter consisted of delicate, but firm, yellow vegetations, along the line of closure of the mitral valve and a few vegetations on the aortic valve.

The microscopic examination of the nodes showed the typical Sternberg-Reed histology.

Emulsified material from the nodes was inoculated intravenously into two chickens, subcutaneously into four guinea pigs and one rabbit. One of the chickens died within a few days after injection before any typical lesions could develop. The second bird lived ten months and at autopsy showed extensive tuberculosis of liver and spleen.

Of the four injected guinea pigs, one lived six months; another eleven months; and at autopsy both of these animals showed generalized tuberculosis, involving extensively the lymph-nodes and bones.

Cultures from the lesions on egg media produced a growth of acid-fast bacilli with the cultural features of the avian strain of tubercle bacilli.

The remaining two guinea pigs are still alive, eighteen months after inoculation, which speaks strongly in favor of an avian tubercle infection. The rabbit lived eleven months and the autopsy revealed a peculiar nodular tuberculosis of liver and mesenteric nodes.

The experimental and cultural evidence obtained in this case further strengthens the theory that the characteristic histological picture of Hodgkin's disease is found as the result of infection with the avian strain of tubercle bacilli.

Discussion.—These accumulated data seem to justify the conclusions that many of the recorded cases of Hodgkin's granuloma are atypical tuberculosis and that if the experimental animal inoculations of such material were pursued consistently along the lines of recent investigation it would determine the nature of at least one form of clinical Hodgkin's disease.

Furthermore, the results obtained in the case previously reported, of Pel Epstein's type of Hodgkin's disease, confirms the theory of the tuberculous origin of this disease and suggests the etiological factor to be the avian type of tubercle bacillus.

Having become convinced that the avian tubercle bacillus was the

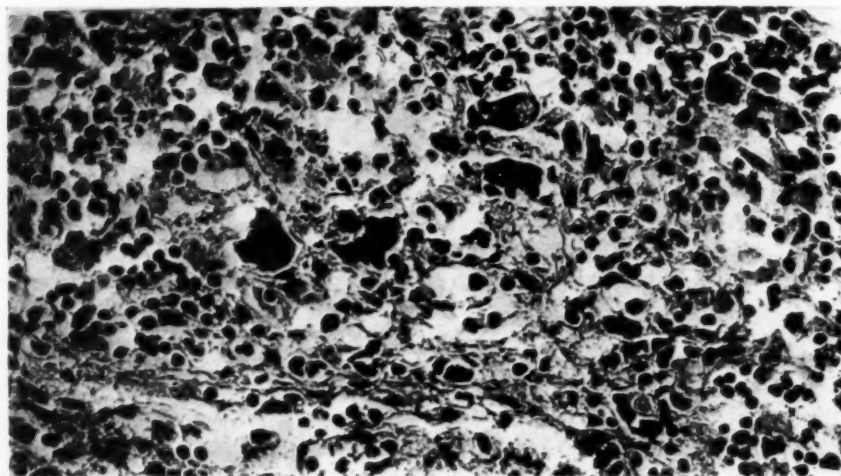


FIG. 1.—Case III.

etiological agent in certain forms of Hodgkin's granuloma, it seemed logical that reactions, analogous to those observed with Koch's old tuberculin, could be obtained by testing cases of Hodgkin's disease with avian tuberculin.

This supposition was further strengthened by the reported observations of Lowenstein and others, that avian tuberculin is specific for avian tuberculosis and does not react to human or bovine infection.

Therefore, a standard tuberculin was made from glycerin broth culture of avian tubercle bacilli, and cutaneous tests with avian tuberculin on cases of suspected Hodgkin's disease were carried on. The technic was the same as with Koch's old tuberculin and both the Mantoux and von Pirquet methods were used.

Seven cases from the Cornell Clinic were tested. Of these four had lymphadenopathy, either generalized or localized in the cervical region. In two of these four cases biopsy showed the typical histology of human tubercu-

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losis and they gave a negative avian reaction with a strongly positive old tuberculin test. One of the remaining two cases, with generalized lymphadenopathy, had a blood picture of leukæmia, and the test was negative. The fourth case had a single suppurating axillary node and smaller nodules in the skin with extensive involvement of scapula. As no biopsy could be obtained, the probable clinical diagnosis was sarcoma. The avian tuberculin test was negative.

A fifth case proved, on histological examination, to be a lymphosarcoma, and gave a negative avian tuberculin reaction.

The remaining two cases were particularly interesting in that they both were unusual forms of Hodgkin's disease. One of them gave a history of recurring attacks of chills and fever over a period of eighteen months, associated with enlargement of cervical axillary and inguinal nodes.

Histological examination of inguinal node revealed fibrosis, no necrosis or typical tubercles with an occasional myeloid giant cell. This was unconvincing, but it is a well-known fact that inguinal nodes are unsatisfactory for biopsy examination, for the reason that so much fibrosis usually exists that the true character of the lesion cannot be determined. Avian tuberculin tests were strongly positive. Old tuberculin tests were less positive.

The other case was a rare form of Hodgkin's disease of the skin with associated involvement of cervical and axillary nodes. The lesions both in the skin and lymph-nodes gave the histological picture of Hodgkin's granuloma. A positive reaction to avian tuberculin was obtained and a less marked one to Koch's old tuberculin.

Five cases of suspected Hodgkin's disease have been tested with avian tuberculin at the New York Hospital.

In two of the cases which occurred in children, the biopsy diagnosis was atypical tuberculosis. Both of them gave strongly positive avian and Koch old tuberculin tests—the avian, however, much more pronounced than the human.

Of the three remaining cases, one showed extensive involvement of cervical and mediastinal lymph-nodes. In the other, the abdominal nodes were the distinctive lesion. These two cases histologically were diagnosed as atypical Hodgkin's disease, or possibly lymphosarcoma. In both of them the avian tuberculin reaction was strongly positive, the reaction to human tuberculin less definite.

The remaining case proved to be a thyroglossal cyst, and in this also a positive avian tuberculin reaction was obtained.

Recently a voluntary communication was received from Doctor Woolley of the Loomis Sanatorium in which he reported a positive avian and a negative human tuberculin reaction in a case of Hodgkin's disease, in which the diagnosis was verified by histological examination.

The findings in this short series of avian tuberculin skin tests, although suggestive, are not convincing. In twelve cases of suspected Hodgkin's disease, positive avian tuberculin reactions were obtained in seven of them.

Four of these were histologically characteristic of Hodgkin's disease. Of three remaining, two showed atypical tuberculosis on microscopic examination of the nodes, and the third was a thyroglossal cyst of the neck. (The most reasonable explanation for the positive avian tuberculin reaction in this last case seems to be the presence of a latent, or healed avian infection.)

Five of the twelve cases were negative to avian tuberculin. On histological examination, two of these proved to be typical human tuberculosis, one a lymphosarcoma, another a sarcoma of the scapula. In the fifth, the microscopic picture was not characteristic of Hodgkin's disease, but more nearly approached that of a lymphosarcoma.

The fact that in many cases both the cutaneous test with old tuberculin and with avian tuberculin are positive, raises the question of the specificity of these reactions. Lowenstein and others believe that the two reactions are specific, that is, each dependent on a separate infection by the respective microorganism.

However, from our experience with this limited number of cases, we are not impressed with the specificity of the avian tuberculin reaction in Hodgkin's disease, but it is possible that the specificity may depend on some hitherto undetermined factor inherent in the microorganism, and with this in mind further investigations are now being carried out to determine, if possible, the nature of this specific antibody.

This summary of my studies is presented in considerable detail in order to show that the accumulated evidence presents substantial proof of the etiological significance of the avian tubercle bacillus in certain clinical forms of Hodgkin's disease.

It is peculiarly gratifying to me to record that the inspiration for this study was derived directly from the influence of Doctor Ewing's concept of the tuberculous nature of Hodgkin's disease.

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THERAPY OF SPONTANEOUS MOUSE CANCER

FAILURE OF TUBERCULIN, KARKINOLYSIN, AND SOME INORGANIC COMPOUNDS THEREIN

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FROM THE STATE INSTITUTE FOR THE STUDY OF MALIGNANT DISEASE

WE HAVE previously used groups of dyes and other organic compounds derivable from coal tar in the search for clues to therapy of the spontaneous mammary tumor in mice.¹ In these papers reasons are given for attempting work so little promising. The later paper contains citations to the literature.² These lead to the chief contributions covering the attempts at therapy of animal cancer.

While we believe all chemical elements in their simplest available forms should be proved with respect to possible influence on animal cancer, the rather miscellaneous group of inorganic compounds here considered was chosen for a more specific reason. Nearly all of them, or similar compounds, have been shown by Ishiwara³ to exhibit in various degrees a tendency to inhibit the growth or cause degeneration of the transplanted tumor in mice. He divided the elements concerned into four ascending groups based on their effectiveness. The first, whose twenty-two elements had no effect, nevertheless contains seven which various workers have at times recognized as tumor inhibiting. The next two groups contain respectively twelve and seventeen elements. The fourth group, showing most unequivocal effect, consisted of six; caesium, germanium, selenium, cerium, scandium and ytterbium. All these elements, and especially those of the last group, demanded further investigation with respect to their effect on cancer, since they influenced propagable tumors in a way which might be useful therapeutically. Nevertheless, having in mind the lability of propagated tumors in general, we were not optimistic that Ishiwara's results would hold for spontaneous growths.

The recent interest in the relation of cancer to tuberculosis, and the use of tuberculin in advanced cases of human cancer, led us to look to animal cancer for some basis for a tuberculin therapy. The treatment being experimental, with human patients only cases far advanced and of the worst prognosis are selected, and the dangers of the tuberculin itself require conservative dosage. From an experimental standpoint the use of mice gave important advantages in that large doses could be given, very early growths treated, and the treatment continued intensively over long periods.

The Inorganic Compounds.—Most of the materials were supplied by the American market and were in every case of the highest purity obtainable. We are highly indebted to Professor B. S. Hopkins, of the University of Illinois, for salts of the rare earths samarium, neodymium, lanthanum and

yttrium. The first three of these were unobtainable in the market. We could find no source of supply for the desired ytterbium, and substituted for it the closely related samarium and neodymium. The scandium salt used was purchased from Adam Hilger, Ltd., of London, being a highly purified product prepared by Sir William Crookes. The columbium salt was furnished through the kindness of Dr. C. W. Balke, of the Fansteel Products Company.

Our aim was to repeat with spontaneous tumors those therapeutic applications of Ishiwara in which he reported some success with transplanted tumors. Of the thirty-five elements which he names in this connection we have used thirty-three—all except ytterbium and iridium. In addition, samarium neodymium, lanthanum and thorium have been tested.

Tuberculin.—The evidence is that the tuberculins, whether preparations of the bacilli themselves, or the filtrates of cultures, are not toxic to normal animals. Our experiments confirm this. Certainly the normal mouse will endure enormous doses. We have not used the large amounts of material necessary to bring about obviously toxic effects. A single dose of fifteen milligrams of an emulsion of bacilli (B. E.), two-thirds of which entered intravenously, followed by nine milligrams more subcutaneously four days later, did not obviously affect a normal male mouse of nineteen grams' weight. As for filtrate 347, and the bovine filtrate, the tabulations show what large amounts may be given daily with impunity. Here the question is left without finding a toxic or lethal dose if such exist in any proper sense. Manifold larger doses would probably be endured. Thus, while we have administered relatively great quantities to very small animals not only free of tuberculosis but little if at all susceptible to it, the experiments do not cover the limiting cases of maximum dosage. Special concentrates would be required.

"Filtrate 347," prepared at the Johns Hopkins Hospital under the direction of Dr. Alan Krause, was furnished us through the helpful courtesy of Dr. Alan C. Sutton, of Baltimore. It is a bouillon filtrate, without preservative, identical with that used experimentally on human cancer patients at the Johns Hopkins Hospital.

Tuberculin B.E. is in the form of dry tablets prepared by Parke, Davis and Company. They consist of dried human and bovine tubercle bacilli, in approximately equal parts, disintegrated by grinding, and mixed with a soluble base. A suspension of the bacillary fragments in distilled water was injected.

Tuberculin T.R. consists of similar tablets prepared by Parke, Davis and Company, from human and bovine tubercle bacilli in approximately equal parts. The bacilli are washed thoroughly in water, ground and mixed with a soluble base. A suspension was injected.

Tuberculin B.F. (Bovine) is a bouillon filtrate made by Parke, Davis and Company. It is preserved with 0.5 per cent. phenol. It was received in and used from one-cubic-centimetre rubber-capped glass bulbs.

Karkinolysin (Hanson) is "a thymic extract, each cubic centimetre representing 0.6 gram of the fresh gland. Average dose one cubic centimetre intramuscularly, once daily. For experimental use only."

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Technic. Explanation of Tables.—The methods were in general the same used in previous work. The solutions were all made with distilled water. The single sample of filtrate 347 was kept carefully aseptic and near the freezing point, and the daily portion was aspirated from a vaccine bottle through the rubber diaphragm stopper, which was never removed. Karkinolysin was handled in the same way. The rest of the material required no especial precautions. No rigid asepsis was used with the injections into mice.

The tumor used was the mammary adenocarcinoma in the albino mouse, spontaneous in every case. Injections were often continued almost to the death of the animal, and far beyond a stage where regression seemed possible. The terminal cachexia was often accompanied by a shrinkage of the tumor. Where the maximum size of the latter did not occur at end of treatment or at death, it is indicated in the last column, as is the development of a second tumor during treatment.

For the inorganic compounds it was aimed to give as high a dose as could be continued daily for a long period without loss of body weight. Every chemical therefore has been used at or near the maximum dosage. In

TABLE I
Inorganic Compounds

1. Ammonium vanadate	29. Potassium bifluoride
2. Antimony potassium tartrate	30. Potassium borotartrate
3. Arsenic pentoxide	31. Potassium columbium oxyfluoride
4. Beryllium carbonate	32. Potassium fluosilicate
5. Bismuth potassium iodide	33. Rubidium chloride
6. Boric acid	34. Rubidium hydroxide
7. Cadmium acetate	35. Ruthenium chloride
8. Cæsium aluminum sulphate	36. Samarium nitrate
9. Cæsium chloride	37. Scandium potassium sulphate
10. Ceric sulphate	38. Selenious acid
11. Cerous chloride	39. Silicic acid
12. Cerous oxalate	40. Sodium fluoride
13. Cerous sulphate	41. Sodium selenate
14. Cobaltous iodide	42. Sodium silicate
15. Cobaltous chloride	43. Sodium tellurite
16. Germanium dioxide	44. Sodium vanadate
17. Gold sodium chloride	45. Stannic chloride
18. Hexammincobalt chloride (Luteo-co- balt chloride)	46. Strontium chloride
19. Indium trichloride	47. Telluric acid
20. Iron chloride (ic)	48. Thorium nitrate
21. Iron salicylate	49. Titanium potassium oxalate
22. Lanthanum nitrate	50. Uranyl nitrate
23. Neodymium nitrate	51. Uranyl chloride
24. Palladium chloride	52. Vanadium chloride
25. Palladium sodium chloride	53. Yttrium nitrate
26. Phosphoric acid (meta)	54. Yttrium nitrate (Hopkins)
27. Phosphorous acid	55. Zinc acetate
28. Platinic acid, chloro-	56. Zirconium nitrate
	57. Zirconium oxychloride

TABLE II
Inorganic Compounds

Serial	Per cent. of solute	Dose— mg. or ml.	No. of doses		Duration— days	Survival— days	Total dosage— mg.	Weight of mouse—gm.			Diameter of tumor—mm.			Remarks
			Intrav.	Subc.				Begin- ning	End	Death	Begin- ning	End	Death	
1	.05	.1	53	23	23	29	2.3	33	30	24	11.	15.	14.	Maximum 19 mm. A second tumor arose.
2	.05	.05	4	4	57	58	2.8	22	23	20	7.	16.	15.	
3	1.	1.	10	6	25	26	25.	28	26	26	13.	16.	16.	
4	.0625	.0625	16	25	41	103	41.	25	26	21	9.	12.	13.5	Surviving. A second tumor arose. Three tumors. All grew.
5	Sat.	.5 ml.	76	12	88	89	5.5	28	27	27	8.	16.	16.	
6	2.	5.	27	16	43	49		31	33	24	8.	25.	21.	
7	Sat.	.2 ml.	4	26	30		150.	28	28		9.	14.		Surviving. Maximum 17 mm. Maximum 11.5 mm.
8	4.	12.	53	3	56	106		31	34	31	6.5	23.	28.	
9	4.	12.	34	34	34	35	408.	29	28	28	4.	9.	26.	
10	.1	.25	74	3	77	79	924.	26	27	24	9.5	28.		Surviving. Maximum 17 mm. Maximum 11.5 mm.
11	.5	.5	12	9	21	22	5.25	29	23	23	9.	11.	11.	
12	.05	.05	11	43	54	56	27.	27	28	22	9.	13.	13.	
13	.05	.05	28	48.	78		3.9	26	27		7.5	18.5		Missing.
14	2.5	5.	36	1	37		185.	28	23		8.5		15.	
15	Sat.	.2 ml.	34	5	39	50		27	31	27	10.	29.	32.	
16	.01	.01	25	6	33	35	.31	27	18	16	6.5	7.	7.	Missing.
17	.05	.1	29	22	52	78	5.1	30	35	37	7.5	33.	37.5	
18	.05	.05	21	16	37	39	1.8	28	21	21	11.	16.	13.5	
19	.05	.25	15	32	47	53	11.7	36	31	31	10.	19.	19.	Missing.
20	.25	.25	21	21	22	22	5.25	32	27	25	13.	17.	16.	
21	.25	.125	34	14	50		6.	30	27		7.	17.	17.	
22	.25	.5	58	58	58	63	27.	29	25	18	14.5	23.5	21.	Missing.
23	.25	.5	22	61	83	84	41.5	26	23	21	6.	11.5	10.	
24	.135	.135	35	33	68	69	9.1	26	23	20	7.	12.5	12.5	
25	.2	.4	14	47	62	97	24.8	29	27	28	19.	27.5	27.	Missing.
26	Sat.	1. ml.	15	9	24	26		31	30	25	10.	16.	14.	

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17	.025	.05	10	27	46	93	2.3	27	29	21	11.	17.	21.
	.025	.05	48	14	62	63	3.1	30	24		5.5	11.5	18.5
18	.05	.05	46	2	48	50	2.4	29	24		13.	18.5	15.
19	.03	.03	21	19	40	41	1.2	27	28		9.5	15.	19.
20	.009	.009	15	26	41	119	.36	29	28	21	9.	16.	19.
21	2.5	5.		34	34	64	170.	28	29		6.	12.	19.
22	.04	.006	21	58	79	80	3.16	23	21	10	6.	14.5	
	.006		35	12	47	49	.28	27	18	18	5.	10.	
23	.2	.2	20	23	43	45	8.6	28	22	21	6.	17.	17.
24	.25	.1 ml.		44	46	24	22.	25	24		4.	7.	
	Sat.			24	24	24		28	25	25	9.	11.	11.
25	.1	.4	3	27	30	20	12.	28	25	18	4.5	6.	5.5
	.1	.3	3	14	17		5.1	30	24		4.	6.	
26	.4	.4	35	44	88	89	31.6	25	24	22	6.	10.	
27	.5	.5	17	28	45	46	22.5	29	25	25	15.5	12.5	20.
	.5	.5	11	30	41	42	20.5	29	24		7.5	10.5	10.5
28	.05	.1	17	44	62	72	6.1	26	27		8.5	16.	17.
29	1.	.5	22	11	33	53	16.5	28	29	23	9.	23.	24.
30	Sat.	.25 ml.	20	13	33	40		27	27	18	10.	18.	15.
31	.1	.1	31	44	44	63	4.4	28	30		7.5	27.	17.5
	.05	.1		24	55		5.5	24	24		6.	17.5	
32	.1	.1	44	32	78		7.6	29	25		4.	7.5	
33	1.	4.	40	71	72	128	28.4	25	30	36	7.	15.	27.
	1.	4.		22	64	130	24.8	32	31	25	6.	13.	29.
34	.6	.6	12	25	37	38	22.	23	24	24	10.	23.5	23.5
35	.01	.03	29	12	41	58	1.2	26	28	23	7.8	20.	22.
36	.5	.5	16	20	36	37	18.	29	22	10	7.5	12.5	11.
	.5	.5	9	34	43	44	21.5	27	26	24	11.	15.	14.
	.05	.05	40	15	55	56	2.75	25	25	22	11.	24.5	22.5
37	.1	.2	12	40	52	53	10.4	25	25	22	9.5	14.	14.
	.1	.1	21	45	66	67	6.6	31	29	27	7.	10.	10.
	.01	.01	31	23	54	55	.54	26	31	30	9.	33.	33.

Maximum 19 mm.
Surviving.
Surviving.
A second tumor arose.
Maximum 24 mm.

Missing.
Surviving.

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TABLE II (Continued)

Serial	Per cent. of solute	Dose— mg. or ml.	No. of doses		Duration— days	Survival— days	Total dosage— mg.	Weight of mouse—gm.			Diameter of tumor—mm.			Remarks
			Intrav.	Subc.				Begin- ning	End	Death	Begin- ning	End	Death	
38	.025	.05	25	24	49	57	2.4	31	29	21	11.	14.5	12.5	
39	.1	.2	32	1	40	43	6.6	25	23	21	9.	15.	15.5	
40	.5	.5	29	15	44	47	22.	30	22	20	8.	15.5	12.	
	.5	.5		37	38	40	18.5	28	22	22	7.	10.		
41	.1	.1	44	27	73	74	7.1	25	20	19	7.	19.	17.5	
42	1.	2.5	15	18	33	109	82.5	29	30	37	11.5	25.	40.	
43	.025	.05	32	12	44	114	2.2	27	28	24	10.	16.	26.	Maximum 11 mm.
	.025	.05	36	8	44	99	2.2	25	25	24	9.5	10.		A second tumor arose.
44	.1	.1	49		49	50	4.75	25	24	23	7.5	12.	11.	
	.1	.1	22		22	66	2.	27	28	23	12.	16.	23.	
45	.1	.2	10	17	27	20	5.4	27	23	21	7.	8.5	7.5	A second tumor arose.
	.1	.1	23	45	76	71	6.8	26		21	9.	17.	15.5	
46	2.5	5.	18	14	32	34	160.	25	28	24	10.	22.	21.	
47	.2	.05	64	41	105	106	5.25	27	23		8.5	16.5		
48	.1	.05	17	43	66		3.	30	31		10.	20.		
49	1.	.5	16	23	39	73	10.5	30	30	26	10.	15.5	24.	A second tumor arose.
	.125	.25	17	3	20	24	5.	23	19	16	8.5	10.	8.5	
50	.1	.1	20	33	54	56	5.3	29	25	19	8.	13.5	13.	Maximum 14.5 mm. Surviving.
	.01	.01	49	27	78		.76	29	34		7.	29.		
51	.125	.125	18	4	22	108	2.7	30	29	26	7.	11.	26	A second tumor arose. Surviving.
52	.125	.125	15		15		1.8	29	28		5.	6.		
53	.75	.75		35	35	54	26.25	28	32	23	18.	20.	26.	
	.1	.1	15	21	36	37	3.6	25	24	21	5.5	13.	13.	
54	.25	.25	21	24	47	48	11.25	28		20	7.5	14.	14.	
55	.05	.05	52	12	64	85	3.2	32	32	25	7.	16.	16.	
56	.2	.2	8	56	64	76	12.8	28	31	28	8.	21.5	21.5	A second tumor arose.
	.2	.4		39	39	41	15.6	29	24	23	13.	23.	23.	A second tumor arose.
57	.125	.125	4	52	56	57	7.	24	27	22	10.		15.5	Maximum 19 mm.

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addition some mice have been treated with greatly diluted doses. The injections were intravenous when and as long as possible; daily, with some few lapses. With very few exceptions each agent has been tested against a tumor in its earlier stages, of diameter ten millimetres or less. In addition some advanced tumors have been used. Over 270 tumor mice have been sacrificed to the investigation. From these typical cases have been selected for tabulation in detail.

The inorganic compounds are listed alphabetically and numbered serially in Table I. Table II refers by serial number to this list. Each line represents one animal. Based on the anhydrous salt, the percentage of the solute is stated and the dose in milligrams of the solute. From these the volume injected, commonly 0.1 millilitre, may be reckoned. For the few saturated solutions the dose is given in millilitres and the total dosage not carried out. "Duration" means the interval between the first and last doses; "survival," the interval from first dose to death of animal. Other headings explain themselves. In a few cases, on account of slight toxicity or solubility, saturated solutions were used, the exact content undetermined; and in a few others, where a precipitate remained, as by hydrolysis, the solution was shaken and a uniform suspension included in the injection. The doses of iron salicylate, not appreciably soluble, represent merely subcutaneous deposits of the salt.

We had the assistance of Dr. Lydia M. Gibson in administering the inorganic agents.

Table III gives the details for tuberculins and karkinolysin. The tuberculin tablets were spread in distilled water and each dose was contained in 0.3 to 0.6 millilitres. Filtrate 347 was diluted with distilled water for the smaller doses and 0.1 millilitre volumes injected. The larger doses, and the bovine tuberculin, were given undiluted. Except in two animals, all tuberculin doses were subcutaneous. Doses were given daily or at nearly uniform intervals, which appear from the tabulation.

Controls.—While the transplantable tumors may regress and disappear and the host die of old age or intercurrent disease, it is well known that mice bearing the spontaneous tumor almost never recover. Recovery is practically an unknown phenomenon. The tumor, however, may fluctuate in growth rate or remain stationary; and even a degree of regression is well established. According to Woglom¹, about one per cent. remain stationary or regress. Complete disappearance followed by recurrence has been observed. It is not easy to identify a growth histologically and follow it to complete absorption, but the cases of regression imply the existence of spontaneous cure, however rare. We have seen none. The survival of the mice after a tumor becomes palpable varies within a wide range; three or four months is a probable average. The tumor grows slowly or rapidly and is rarely stationary. The larger tumors almost always ulcerate, the smaller ones occasionally.

TABLE III
Tuberculin; Karkinolysin
 Tuberculin B. E. 1 mg. and .0001 mg. tablets

Number of doses	Duration of treatment—days	Survival—days	Total dosage—mg.	Weight of mouse—gm.			Diameter of tumor—mm.			Remarks
				Beginning	End	Death	Beginning	End	Death	
Dose: 1 milligram. Subcutaneous										
14	39	76	14	27	27	23	12.	17.	20.5	Surviving. Pregnant at beginning.
13	36	39	13	26	26	19	13.	16.5	15.	
10	17	130	10	24	25	22	7.5	7.5	27.5	
85	87	88	85	29	25	23	7.	17.	16.	
98	102		98	43	29		6.5	11.		
9 intravenous, 4 subcutaneous, doses										
13	13	24	13	25	26	23	11.5	16.	17.5	
Dose: 0.0001 milligram. Subcutaneous										
56	68	92	.0056	27	26	20	4.5	7.5	9.	Max. 22.5 mm.
56	59	60	.0056	25	21	20	12.5	21.	21.	
66	69	77	.0069	28	28	24	15.5	26.5	24.5	
Tuberculin T. R.										
Dose: 1 milligram. Subcutaneous										
17	33	46	17	24	27	24	7.5	24.	26.5	

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Dose in millilitres Number of doses					Duration of treat- ment— days	Survival— days	Total dosage— ml.	Weight of mouse—gm.			Diameter of tumor—mm.			Remarks
.001	.01	.1	.4	.5				Begin- ning	End	Death	Begin- ning	End	Death	
Filtrate 347. Subcutaneous														
22	25	17			42	120	1.95	39	39	9.5	12.5	15.	A second tumor arose. Surviving. Tumor 20 mm. Max. 15 mm. Max. 22 mm. Second tumor arose. Max. 17 mm. Second tumor arose. Enormous metastases.	
	25	17			42	67	1.95	31	36	9.5	22.	24.		
	25	17			42	52	1.95	25	24	6.	8.	9.5		
	25	17			42	17	1.10	31	26	11.	11.	19.5		
	16	17			16	123	1.7	34	23	15.5	12.	14.		
		17			31		.622	24	25	9.	10.	17.5		
			18		22	27	7.2	30	34	10.	19.5	20.		
				10	18	38	5.	36	34	8.5	10.	9.		
Intravenous														
	17	17			34		1.87	25	25	7.	12.5			

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Tuberculin B. F. (Bovine)

Number of doses	Duration of treatment—days	Survival—days	Total dosage—ml.	Weight of mouse—gm.			Diameter of tumor—mm.			Remarks
				Beginning	End	Death	Beginning	End	Death	
Dose: 1 millilitre										
30	30	32	30	28	23	21	14	20	15.5	
Dose: .5 millilitre										
66	68		33	31	32		6.5	7.		Max. 9 mm. Second tumor arose.
Doses: 28 at 1 ml.; 57 at .5 ml.										
85	90	93	56.5	29	21	18	3.5	7.	6.	Max. 8 mm.
Karkinolysin (Hanson)										
Dose: 1 millilitre										
15	15	16	15	22	20	19	9.	11.	10.5	Rapid growth. Second tumor arose.
29	29	30	29	31	31	27	10.5	26.5	27.	
62	62	67	62	34	31		10	19.5	20.	

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Mice will endure enormous doses of distilled water and still more of physiological salt solution, whether intravenous or subcutaneous. Data have been published and are not repeated here. As our results are all negative, controls need no detailed consideration.

Results.—Since the tumor varies widely in rate of growth, it was to be expected that slowly increasing or nearly stationary growths would suggest restraint imposed by the medication. Numbers of such cases occurred. All of them have been checked by repetition until without exception every agent has been tested with a tumor whose growth was unequivocal. The tumors may be said to have run their usual course, and often to ulceration.

We are not able to find any evidence of therapy, or even definite effect—macroscopic or microscopic—on the tumor or its growth. The illusory nature of the apparent success which has sometimes followed attempts at therapy of propagated tumors is again implied. Such growths are not fit indicators of the therapeutic value of presumptive cancer treatments.

SUMMARY

Fifty-six inorganic compounds, containing thirty-three chemical elements for which there is evidence indicating therapeutic value for transplantable cancer, have been tested for their effect on spontaneous mouse cancer.

Four forms of tuberculin and one extract of thymus have likewise been tested.

No therapeutic action was exhibited by any of these.

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SUSCEPTIBILITY AND RESISTANCE TO TAR CANCER

AN EXPERIMENTAL STUDY

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THE clinic and the laboratory are two methods of equal value for the study of cancer. Nevertheless, certain domains of cancerology are more easily studied in a laboratory. That is why the study of tar cancer is so instructive in enabling us to follow in an easier way the early development as well as the evolution of the disease, and to study the action of a multitude of factors which could be of influence on its relation and evolution.

The object of this article is not to make an entire study of the matter—not even a bibliographic study of the problem. What we desire is to give an account of our experiences in studying the part played by the organisms as a whole in the etiology of tar cancer. In the latter one, as in any other cancer, there are in reality determining local factors and a general organic resistance. Certain authors believe that the local factors, called the irritating factors, are of physico-chemical order; others are inclined to think that they are of infectious nature, infection the bed of which has been prepared through local irritation. The general organic receptivity concerning tar cancer is no longer debatable. The point is now to determine the importance of the organic receptivity for the germination of the cancer and to establish, if possible, the nature of this receptivity. Concerning particularly the tar cancer, we should like to show how far we have come in this study.

Demonstration of the Existence of a Predisposition to Tar Cancer.—It will be remembered that the first scientist who proved the existence of a species, racial, individual and even a singular predisposition (receptivity) against experimental spiroptera-cancer, is Fibiger. His experiments are models of classic studies for cancerologists.

Lipshutz, and later, in 1922, Roussy, during the first gathering of the "Leewenhock Vereeniging" drew attention to the fact that all the mice submitted to the same tarring did not produce cancer equally. Some animals seem to be quasi refractory to it.

Later, Bang and Leitch have shown that a tar-cancer sprang up in a mouse several months after the cessation of the tarring (the quasi specific irritation of Teutschlaender). The final outbreak of the cancer process has thus nothing to do with the actual presence of the tar itself. The tar is necessary as a quasi specific irritating factor for the preparation of the soil, but after this is done the process goes on without it. One could say that it has put into motion a mechanism the end-result of which is the cancer. This being so, we have asked ourselves if this fatal and slow work of cancerization of the cell is influenced by the metabolism of the individual.

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Since 1923, we have shown that the tarring is modifying the organic medium to such a degree that this alteration contributes to the development of cancer. In fact, if we painted the necks of a series of animals during a short period (two months, for instance) only a few animals would develop cancer—approximately 20 per cent. But if we continue the paintings on another region, at a certain distance from the former one, for two months more, we see that a much greater number of animals (71 per cent.) produce cancer on the first area painted. With Masse, I have shown afterwards that by injecting tar in small amounts under the skin of the abdomen of a series of mice during three to four months, carefully avoiding soiling the skin surrounding the injected point, we prepare the animal organism to produce cancer of the skin at a distance far from the injected spot: If we paint the injected animals on the neck during two months we produce a large percentage of cancer (58 per cent.) while the controls (painted the same time but not injected) present only 15 per cent. of cancer. Another series of controls, painted at the same time during a period of two and one-half months, gave only 30 per cent. of malignant growths. Moreover, several cases of "spontaneous" mammary cancer developed among the injected animals not bearing skin cancer and the skin cancers develop earlier and are more malignant than those of the control animals (50 per cent. of metastasis among the injected, 20 per cent. among the controls).

Merteus, in the same order of ideas, established that the papillomas and the "histological cancers" of the ear of a rabbit regress if one stops the tarring of the diseased ear, but the same kind of tumors continue their growth if one paints the other ear.

Since that time our researches have been confirmed by Beck, Fischer-Waesel, Soboleva, Schwabad and Schov, Kreyberg, and some others. Kreyberg was able to produce cancer with metastasis in animals poisoned with tar only by burning their skin. Lynch, in the laboratory of Murphy, has increased in a considerable proportion the percentage of spontaneous tumors of the lungs in a susceptible strain of mice painted various times with tar, a very short period on each spot, in order to avoid the apparition of skin cancer. The tumor age of those animals was also markedly lowered.

So it appears duly established that the alteration of the animal metabolism as the result of chronic intoxication by tar, contributes to the elaboration of cancer on chronically irritated spots.

The Rôle of Certain Metals in the Predisposition to Tar Cancer.—It would be impossible to study here the action of all the metals which have been tried in various laboratories. We shall speak only of those which have been particularly studied in this institute.

One of our pupils, P. Estas, has, at our request, been studying the action of copper and has established the fact that when used in feeble doses it has a retarding effect on the development of tar cancer as well as on

its evolution. When used in strong doses, the metal, which is very toxic, has quite the opposite action.

Sensational affirmations having been spread about, we have asked Estas to study the action of magnesium. We used magnesium sulphate in injections, the animal of experiment being the mouse, as it is the only kind that easily makes tar cancer of a real malignant character (physiological cancer, following our terminology). The details of these researches are consigned in Estas' thesis; we state here only the conclusions of it: Magnesium given in suitable doses is capable of delaying the apparition and the evolution of the tar cancer in the mouse. To obtain a real effect one must give at least one centigram a week to a mouse. Delbet believes that magnesium chloride is more effective. Honoré, one of our pupils, was able with this salt to confirm Estas' results.

Consequently, it seems established that certain metals when introduced in suitable doses in the metabolism of diseased individuals are capable of influencing the development and evolution of tar cancer by retarding them.

We have asked ourselves also whether certain other metals should not have quite an opposite action.

It is well known that certain authors attribute to arsenic a rôle in the evolution of cancer (accelerating action). In the different experiments we have tried to elucidate this rôle but have not succeeded, so that we cannot have a personal opinion on the matter. *Per contra* we have studied the action of different radioactive substances, especially the action of ionium and the action of a composed salt of thorium-uranium. We have chosen those substances out of the radioactive series because they have practically a constant and weak radiancy and also because they issue only particles. So we have to pay attention only to a sole type of radiation quasi entirely absorbed by the cells where the radioactive ion has its abode. We may also inject relatively considerable doses without provoking an aplastic anæmia. When we inject those metals intravenously, they settle first in the reticulo-endothelial system. On account of the great energy of the particles one can suppose that they have an influence on the metabolism of the system. Those particles form an energetic power of synthesis for the hydrocarbons (Mund) and they are able to transform ergosterol into the antirachitic vitamine D (Maisin, Pourbaix, Mund, Castille).

At any rate, the animals which have had strong doses of ionium before the tarring and those which have had only a small quantity during the paintings produce cancer more easily than the animals of control which have not been treated by ionium and their cancers are more malignant.² The results are as follows:

We have shown with Ledecq and Estas that ionium has the same effect on rabbits. Since the experiences of Tamagiwa and Itchikawa, and especially since the work of Leroux, we know that tar cancer in rabbits is seldom progressive. It regresses and disappears easily after the cessation of the tar painting. It is those cancers we have called "histologic can-

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Absolute Percentage of Cancer

Number of days	Injected per cent.	Controls per cent.
150.....	40.6	18.7
210.....	78.1	56
End of experiment.....	87.5	72.9

N.B.—We call “absolute percentage of cancer” the percentage of animals producing cancer among those which have lived after the appearance of the first cancer in the series of animals.

cers” in opposition to progressive and metastasizing cancers which we have called “physiologic cancers.” A great number of our rabbits injected with ionium produce “physiologic cancer” (more than 30 per cent.) while their controls painted during the same length of time never produce a progressive cancer but only “histologic cancers.”

We have obtained similar results with injections of ionium in fowl (production of large embryoma in injected chicken, and even malignant tumors—Maisin and Dupuis).

In 1929, Spies and Picard studied in our institute the effect of Hocking's fluid (a composed colloidal salt of uranium-thorium) on a grafted mouse tumor. They found that this compound accelerates the tumor growth.

We believe that the action of some metals on the development and evolution of tar cancer is quite an established fact. Certain metals have a retarding action, others, an accelerating effect. The mechanism of those actions is not yet understood and can be elucidated only by experiment. At the end of this work we shall discuss the matter.

The Rôle of Certain Physiologic Functions in the Predisposition to Cancer.—It is absolutely necessary before speaking of some of these functions in particular to consider the question briefly in a general way.

In fact, one can conceive the action of certain physiologic functions on the cancer from two different points of view. Some of these functions could have an effect on the local determinism of a tumor. For instance, disturbance of the lactation, as Bagg showed it, could provoke congestion and chronic inflammation in the mammary gland of the mouse and cause the apparition of a breast cancer in susceptible animals. Various stasis of organic fluids could, as it appears, lead to the same result. Considering this from the physiologic point of view, concerning the interaction existing between certain glands with internal secretion, one must remember the interesting communication of Goormagtig showing that repeated injections of folliculin are capable of producing adenoma of the breast in mice. On the other hand, it is impossible to deny the action of the ovaries on the development of uterine fibroma. It seems probable that other similar facts will be proved in the future for other tumors.

At any rate, these influences are acting as local determining factors on the development of a tumor in a predisposed individual at any given spot. Considering another point of view one could ask whether certain organic

functions, as, for instance, the metabolism of fats or of the nucleoproteids, are injured in animals predisposed to cancer and whether those lesions should not be one of the important factors in cancer predisposition.

It is from this point of view that we have been studying the testicular function of mice in its connection with cancer and recently the function of the thymus and also the metabolism of fats.

In 1925, we pointed out with Desmedt and Jacqmin the particularly rapid evolution of tar cancer of a group of castrated mice which had given a considerable percentage of metastasis. I have asked Jacqmin to continue the study of that question. In his thesis he confirms these first observations. A point quite established during the researches of Jacqmin is one showing that mice castrated before puberty are not at all refractory to tar cancer as they are refractory to implantation of transplanted tumors (Strong, Murphy). One could even assert that those mice are more susceptible than normal mice of the same age and strain, tarred at the same time; the percentage of cancer and of lung metastasis is higher than in the control group.

For several years one has considered the thymus played a rôle in the genesis and evolution of cancer. Fichera was one of the first to study this question. Recently, Babes, while studying the effect of tar intoxication on rabbits, has noticed a very rapid and marked destruction of the thymus in tarred animals. In the United States, Hanson has been trying the action of certain thymic extracts on human cancer and he relates four cases where he seems to have obtained encouraging results.

In our Institute we have asked Miss François to study that question. She noticed that tarred mice, fed with thymus diet and refractory to cancer, had, in spite of their age, persistence of remnants of thymus abnormality well conserved, thymus which has almost entirely disappeared in normal animals of the same age and which is non-existent in animals that are bearers of tar cancer. These observations, added to the results obtained by other workers, deserve the attention of cancerologists and suggest new researches in this domain.

We have not had the opportunity of studying personally the action of the suprarenal, the ovaries, the thyroid, the hypophysis and pineal gland on experimentally induced cancer, but several publications have appeared concerning those questions. Nevertheless, I am obliged to mention especially the work of Loeb, pointing out the influence of the ovariectomy before puberty on the development of spontaneous breast cancer in mice as well as the recent work of G. Coffey and J. Humber, Arloing and Sokoloff on the influence of suprarenal gland on transplanted tumors and on human cancer.

Influence of Diet on Tar Cancer.—Since the remarkable work of Minot and his assistants showing the influence of liver diet on pernicious anæmia, we have tried the action of various diets on tar cancer. As it is already established with certain evidence that general susceptibility plays an important rôle in the development of cancer, one has a right to think of the diet in trying to modify this susceptibility. In fact, the discovery of Minot, and those

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concerning the different vitamins show how certain food factors have an influence on various affections, which one never thought could be influenced by diet.

(A)—*Influence of the Liver Diet on Tar Cancer.*—In 1928, we published with Miss François our results concerning the action of the liver on the genesis and the evolution of tar cancer. We showed that mice submitted to this diet produce the cancer more quickly and in a higher percentage than the animals of control. These cancers are very malignant and produce a high percentage of lung metastasis. Since that time, Miss François, continuing the study of this question, has several times repeated the same experiment. If one makes the total out of the number of animals that have been living long enough to produce cancer, one reaches the figure of 113 for animals nourished with liver and the figure of 132 for the animals of control which had another diet—either vegetarian or a mixed one of meat and wheat. Being grounded in those important figures, she was able to state that the liver diet activates the genesis of tar cancer and its evolution. These are the principal results of her experiments:

Absolute Percentage of Cancer

Number of days since beginning of experiment	Liver diet per cent.	Controls per cent.
120.....	10	4
150.....	46	17
180.....	69	39
210.....	76	59

Percentage of Lung Metastasis

Liver.....	49.3
Controls.....	29.3

Note.—A certain number of animals being still alive, the percentage of metastasis could still vary, but only within small limits.

The liver diet has the same influence on the tar cancer of rabbits and on the "histological cancer" of the gall-bladder of the guinea pig (Ledecq).

Pushing these researches further, we have succeeded in showing that the active substances resist desiccation and are still contained in the liver powder thoroughly washed with ether in order to extract the fats. Those hepatic fats are quite inactive; perhaps their action is an inhibiting one, but more data is necessary to prove it. The liver extract of the "Nordman Werk" of Hamburg, which is rather active for pernicious anæmia, has a slightly activating effect, but surely less marked than that of liver or liver powder. The extract No. 343 of Eli Lilly (Minot), which is very powerful against pernicious anæmia, is deprived till the 160th day at least, of any activating influence on the development of cancer. The following is the result of this experiment:

J. MAISIN

On the 180th Day Since Experiment Began

	Cancer	Papilloma	Free of lesions
Liver diet	10	4	0
Raw-beef diet (muscles)....	5	8	1
Lilly extract 343	4	6	5

Of all these researches we can conclude that the liver contains stimulating substances. They are resistant to desiccation and not included in hepatic fats. They are not to be identified with the anti-anæmic substance of Minot.

(B)—*Influence of Different Other Diets on Tar Cancer.*—We have already mentioned that hepatic fats seem to have possibly an inhibiting action when compared with a raw-beef-muscle diet or a purely vegetarian one. A brain diet, rich in lipoids, too, seems to have the same action, but more marked. This new statement corresponds to the researches of Suguira and Benedict, who showed that brain diet has an inhibiting action on the growth of a transplantable rat tumor. Our results are based on a smaller number of animals, and for this reason we wish to repeat the experiment before we affirm the above-mentioned results.

Animals nourished on a diet composed of a mixture of flour and raw-beef muscle (forty animals) show a small acceleration in comparison with animals nourished on flour alone or on a diet composed of flour and hepatic fats or flour and brain.

Animals fed with a mixed diet, flour and intestinal mucosa, or a diet of flour and splenic extract of the "Nordman Werk," have not shown any characteristic evolution.

Per contra we should like to insist upon animals fed on a mixed diet, flour and thymus three times a week. By means of this diet we have made two experiments, each one with about fifteen to twenty animals kept alive after first appearance of cancer and controlled by a group of animals fed with a mixed diet of flour and raw-beef muscle. The first experiment has shown a considerable retardment in the development of cancer; the second has given the same result in a less marked degree. If one takes the figures of the two experiments and compares them to the figures of the two control experiments with flour and muscle diet, one notices a real retardation in the development of cancer among the thymus-diet mice.

An extremely curious fact to be noticed is the growth of the cancer of the thymus-diet animals after its beginning. Those cancers grow very well, giving big tumors with a high percentage of metastasis. The action of thymus diet seems to be only a preventive and not a curative one. We are repeating these researches in order to collect more data. I have already mentioned that animals fed with thymus were of remarkable health and that mortality was very low in the course of the tar paintings. Often, two months after tarring, animals which have no tumors show a growing up of hairs on

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Absolute Percentage of Cancer

	150 days per cent.	180 days per cent.	240 days per cent.
Thymus.....	9	18	44
Muscles.....	19	35	55
Liver.....	46	69	81

the level of the tarred spot and their coat is so beautiful that one could believe them to be fresh animals.

(C)—*Tar Cancer and Vitamine A*.—On account of the researches of Burrows, Gasparri, Taiki, Rhoda Erdman and others on the action of vitamine A on the development of spontaneous cancer, on the transplanted mouse cancer and on the growth of cells *in vitro*, we have asked Trigaux to study the effect of this vitamine on tar cancer. We have studied its action by feeding and by injection. We have used the product Y of the Lever Brothers and Company, which contains no vitamine D and is very rich in vitamine A. The mice were fed with a mixed diet—raw muscle and flour. A group of these mice, in addition to the diet, received vitamine A three times a week, at a dose which was the limit of toxicity of the Y product for mice. A second group received the same amount of vitamine subcutaneously. The control animals were fed with the same diet without vitamine A and a certain number of them were given, three times a week, an injection of olive oil in the same amount as the product Y injected in the animals of experiment.

Our present results show that vitamine A introduced as a supplement in the normal alimentation of mice has no retarding effect on the development of tar cancer. On the contrary, this group is in advance when compared with the controls. As for the injected vitamines, we cannot affirm anything with certitude because the mortality was very high and the number of animals which survived the appearance of the first cancer was not a very important one.

GENERAL DISCUSSION

Many years ago it was proven that some hormones have an influence on the growth of tissue. Lately one has shown the influence of vitamine A on the growth. Since the discovery of Minot one knows the action of certain substances contained in the liver on the formation of the red corpuscles of the blood. Recently, Castle seems to have proven that the active substances of the liver are products of a normal digestion of meat in the stomach, products which are stored up in great abundance in the liver.

These substances are consequently of quite a different order from those of vitamine A or C which seem not to be able to form themselves regularly in our organism. They have a certain analogy of origin with vitamine D which can also be formed in our organism under the influence of ultra-violet rays. But, anyhow, it is the first time one suspects that normal products of a normal digestion have an influence comparable to a hormonal influence—

action at a distance on a well-determined function. The growth of different tissues is, therefore, dependent on definite chemical substances secreted by certain glands (hormones) or absorbed (vitamines) or even produced by normal organic functions (digestion).

Certain benign tumors are in connection with organic dysfunctions. Has the cancer, a malignant tumor, infectious or not, any relation with one definite or certain well-known organic function?

We showed at the beginning of this work that the general intoxication of the organism by the tar is playing an obvious rôle in the genesis of the carcinomatous process. Pushing our investigations forward, we wish to show by means of what mechanism this intoxication is acting. We have seen that certain alimentary substances contained in the liver facilitate the apparition of tar cancer; others, like magnesium, certain fats or possibly certain albumins (nucleoproteids) have a retarding effect. On the other hand, injection of radioactive metals activates the apparition of the same tumors. These metals have their abode in different organs but especially the reticulo-endothelial system. Possibly their action is the result of an alteration of a certain function, for one finds less injected substance in the tumor than on the level of most of the internal organs and also because they exert their action on the organism before the apparition of the tumor in order to favor its development.

In that way the action of metabolism on the genesis of tar cancer can in one way be influenced by ingestion of certain substances; in the other way, by alteration of certain functions (radioactive metals, castration, *etc.*). Henceforth, one is asking oneself whether the predisposition to cancer is not the result of the presence of certain substances in more or less abundance in our organism, activating substances on one hand, and inhibiting on the other. These substances can be absorbed, be the result of a sort of alimentary intoxication or proceed from a defective organic metabolism. In the first case, predisposition and resistance might be only transitory while in the second case the predisposition would be a permanent phenomenon.

One could try to examine the problem still nearer by producing other experiments of the same order as those which have been the topic of this article; or else try to solve the question by investigating the chemical modifications which take place in the blood during the production of cancer. In this way, one would still have to establish the relation from cause to effect between those modifications and the cancer.

We have asked Miss Pourbaix, chemist of our institution, to study the variations of the serum of rabbits injected with ionium and those of rabbits painted with tar. She has been following the variations of different groups of substances but has concentrated her efforts especially on the variations of cholesterol, a substance often considered as playing a rôle in the evolution of cancer. She has come to the conclusion that a little before the appearance of tumor and during the evolution of the cancer, cholesterinæmia is very unstable, the variations often being quite marked. It seems that

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animals intoxicated and prepared to produce cancer or bearing cancer show great disturbance of the metabolism of fats and are incapable of maintaining their lipæmia in normal conditions.

All these researches force us to admit that the metabolism is playing an important rôle in the genesis of cancer and incite us to investigate in which way the metabolism is lacking.

CONCLUSIONS

1. Tar cancer is the result of a local irritation as well as of a general intoxication of the organism.
2. Certain mineral salts used in convenient doses are capable of delaying the appearance of cancer (magnesium, copper) and of lowering the percentage of induced tumors.
3. Other salts, for instance, salts of radioactive metals, have quite an opposite effect.
4. Diet can influence the appearance and evolution of tar cancer.
5. The liver diet activates the development of tar cancer.
6. It is probable that other diets would retard its appearance.
7. Vitamine A absorbed in addition to a normal alimentation has no inhibitive effect on the appearance of cancer.
8. Preceding closely the development of tar cancer and during its evolution, the metabolism of fats is deficient and the variations of the cholesterinæmia are marked. The same variations are to be noticed after repeated ionium injections.

EXPERIMENTAL AND CLINICAL STUDIES ON THE TREATMENT OF CANCER BY DICHLORETHYLSULPHIDE (MUSTARD GAS)

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THE experimental and clinical investigation reported herein was suggested to the authors by Dr. James Ewing who while serving at the United States Army Medical Museum during the late war, was impressed by the peculiar and specific nature of mustard-gas burns. There are certain characteristics of the mustard-gas reaction which suggest the use of this chemical in the treatment of neoplastic growths.

The action of mustard gas (CH_2ClCH_2)₂S on normal tissues is well known. Since its introduction in 1917 as an agent of chemical warfare much has been written concerning its pathological effects. Warthin and Weller, in 1919, and the report of the Medical Department of the United States Army, in 1926, give a summary of the more important clinical and experimental studies. The action of mustard gas on human tissues has been extensively studied by many observers. The names of Guthrie, Victor Meyer, Winternitz and Underhill are but a few of the well-known workers in this field. An excellent chapter on the subject of "Burns by War Gases" may be found in the recently published book, "Burns," by Pack and Davis.

A mustard-gas burn is very unlike that produced by heat or the corrosive acids. It differs from the heat burn in that there is no thrombosis of vessels; a more intense amount of œdema occurs; the effect is progressive even at times continuing for five to ten days. The zone of necrosis gradually increases for a period, at which time an equilibrium is reached and repair sets in. The blood-vessels are collapsed and tremendously damaged. Intense leucocytosis occurs.

The more severe effects of mustard gas on human skin are characterized by intense hyperæmia; œdema; the formation of vesicles and sometimes pustules of the surrounding tissues; finally, ulceration of the epidermis. This process is essentially local in its action, is accompanied by a pronounced leucocytic infiltration and is characterized by the relatively long duration of action.

It is our experience that immediately following the application of a drop of the mustard-gas solution to a cancer of the skin there is a temporary blanching of the lesion and surrounding epidermis. If the lesion is covered with epithelium there will be practically no pain resulting from the application; otherwise a burning sensation results. Within two hours following the application of the solution, the blanching and anæmia are followed by a hyperæmia. Within forty-eight hours, œdema and vesiculation are well established. This phase is followed by the processes of beginning repair.

MUSTARD-GAS TREATMENT OF CANCER

For the purposes of carcinoma therapy, we disregard the differences of absorptive properties of the skin in different patients.

In 1927 Doctor Ewing suggested to one of us (Bagg) the study of the effect of mustard gas on experimental cancer in the lower animals. This in turn led to the application of this chemical to certain localities, such as the mouth, bladder and rectum of normal animals, as well as a study of the effect of varying the dosage of the solution upon normal skin.

It is the purpose of this paper to summarize the results of our studies of the effect of mustard gas on normal and neoplastic tissues in the lower animals and to record the history of twelve cancer patients treated by this chemical at the Memorial Hospital.

Methods.—The concentrated mustard gas was obtained from the Depart-

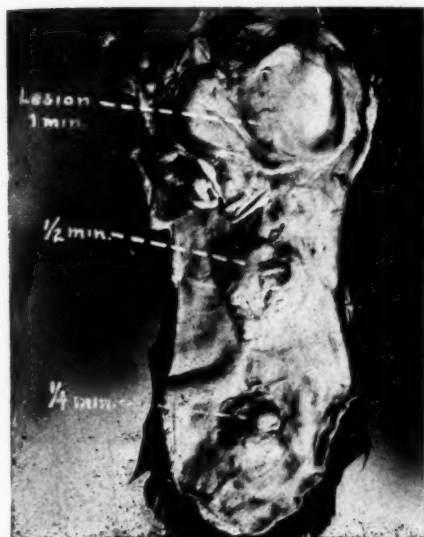


FIG. 1.—The illustration shows the reflected skin of a rabbit. The abscess at the top of the photograph has been cut open and one wall reflected. Upper lesion treated with one minim of mustard gas on surface of the skin. Lesion in the middle resulted from one-half minim and the lower lesion from one-quarter minim. For further details, see text.



FIG. 2.—A mustard-gas eschar is shown with the remnant of a tar cancer in its centre. Animal killed twenty-six days after treatment.

ment of Chemical Warfare Service of the United States Army. Great care was used in handling the solution. The concentrated liquid was kept in a chemical hood and exposed to the air only when the exhaust fan was in operation. The mustard gas was dissolved in absolute alcohol. A small quantity (usually 2 cubic centimetres) was made fresh for each experiment and kept in glass-stoppered bottles. A calibrated glass pipette was used in applying the solution to the surface of tissues. This pipette delivered drops of approximately $\frac{1}{4}$ minim each and this amount was the standard dose used in both the clinical and experimental treatments. Treatments of small animals were made inside the laboratory hood, which carried the fumes away from the operator. We have found that it is well to have all treat-

ments to the larger animals or humans done near a hood, or in a situation where very adequate provision is made for prompt withdrawal of the fumes of the mustard gas. After the treatment, the glass pipette or the syringe was thoroughly rinsed in concentrated nitric acid, which stops the action of the mustard gas. When the mustard gas is applied to the surface of a tumor the absolute alcohol acts as a vehicle, evaporating almost immediately, leaving the mustard gas as a thin film on the treated surface. When relatively small skin cancers were treated, a ring of vaseline was placed near the margin of the tumor to check the spread of the solution too far beyond the limits of the growth.

Experimental Results—Mustard Gas on Tar Carcinoma in Mice.—The scope of this paper does not permit a detailed account of the animal experimentation. A more com-

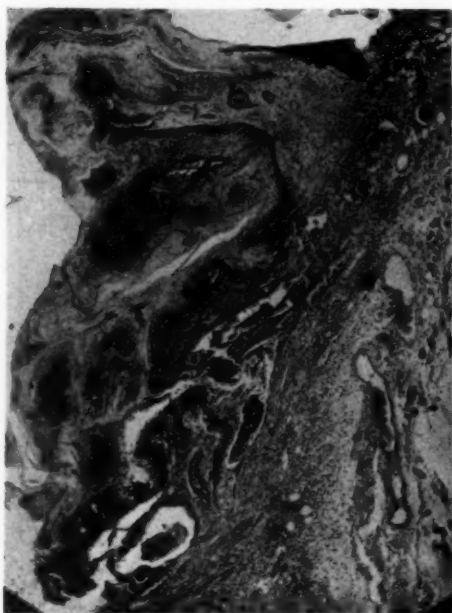


FIG. 3.—Microphotograph of a section through an untreated tar cancer in the mouse.

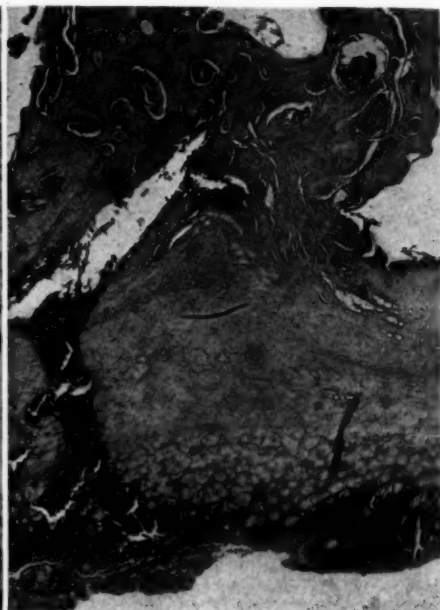


FIG. 4.—Microphotograph of a section through the centre of the lesion shown in Fig. 2. There is apparently complete destruction of the tumor. (Dose, one-quarter minim mustard gas.)

plete report of this phase of the work will be given at a later date. There are certain general deductions which may be drawn from these studies that are of clinical interest and therefore will be mentioned briefly.

It was found that when mustard-gas solution (20 per cent. in absolute alcohol, $\frac{1}{4}$ minim drop) was applied to the skin of the back of an adult mouse there was a severe toxic reaction. The treated skin became tough, thickened and dry. There was pronounced oedema of the subcutaneous tissues and adjacent muscles and the animals died from one to four days later respectively.

When a similar dose of mustard gas was applied to the back of a mouse on which a tar cancer had been previously produced, the presence of the neoplasm itself and possibly the conditions produced in the adjacent skin as a result of long tarring, appeared to protect the animal from the severe general toxic reactions noted when mustard gas was placed on normal skin. Such a reaction was noted in an animal that showed a small

MUSTARD-GAS TREATMENT OF CANCER

papillary growth in the tarred area of the back after seventeen weeks of tarring. At the twenty-seventh week there were three tumors, raised about two millimetres above the skin and covering an area 9 by 15 millimetres. The growth was treated with $\frac{1}{4}$ minim of 20 per cent. mustard gas in absolute alcohol. A heavy eschar appeared which involved the tumor area and adjacent skin. The scab was lost ten weeks later, the skin beneath was apparently normal and there was no local return of the growth. The animal died approximately eleven months after the treatment. Autopsy revealed a metastatic nodule in one lung.

Mustard Gas on Normal Tissues.—In order to test the effect of varying the dosage of mustard gas in relation to the degree of tissue reaction, six skin areas of the back of a large rabbit were treated with varying amounts of a 10 per cent. mustard-gas solution in absolute alcohol. A glass pipette delivering drops of approximately $\frac{1}{4}$ minim was used. The animal was killed two weeks after the treatment, the skin was reflected and the following record shows the dimensions of the resulting lesions:

- Area 1: Dosage, $\frac{1}{4}$ minim mustard gas solution; lesion 20 by 20 millimetres.
- Area 2: Dosage, $\frac{1}{2}$ minim mustard gas solution; lesion 32 by 30 millimetres.
- Area 3: Dosage, $\frac{3}{4}$ minim mustard gas solution; lesion 45 by 28 millimetres.
- Area 4: Dosage, 1 minim mustard gas solution; lesion 50 by 50 millimetres.
- Area 5: Dosage, $\frac{1}{2}$ minim mustard gas solution; lesion 35 by 28 millimetres.
- Area 6: Dosage, $\frac{1}{4}$ minim mustard gas solution; lesion 23 by 16 millimetres.

Fig. 1 shows the reflected skin of the right side of the body and the lesions resulting from $\frac{1}{4}$, $\frac{1}{2}$ and 1 minim doses respectively. The abscess resulting from the larger dose is shown at the top of the illustration. The median wall was cut and reflected to one side. The smaller lesions, as shown in the illustration, were well localized and limited by the fascia of the underlying muscles. The lesion resulting from the 1 minim dose was also largely limited by fascia, but at one point the underlying muscles were superficially involved as well. The animal was killed two weeks after treatment. The lungs, kidneys, liver and other viscera were examined and found apparently normal.

Clinical Experimentation.—The agent was applied to thirteen patients, most of whom were suffering with cancer in one form or other. Brief reports of these cases appear below. They include cases of squamous carcinoma of the skin, melanoma, neurogenic sarcoma, epithelioma of the penis, etc. Twelve of the patients were treated by applying the solution of mustard gas to the external lesion. One patient, a remarkable case, was treated by injecting this solution intratumorally; a terrific reaction resulted but a neurogenic sarcoma several times recurrent has practically disappeared following this violent therapeutic reaction. So that we feel the possibilities of using this agent therapeutically lie not only in external application but also in interstitial doses. In fact, the latter method to date is more impressive.

We fully recognize that this agent has been applied in our cases too recently for us to report cancer cures. But as it takes so many years to report cures we are hoping that such a preliminary report may suggest possibilities to other investigators.

CASE I.—Epithelioma.—Male, F. R., aged thirty-one, a government clerk, seventeen years previously was treated with "Fowler's solution" for nervousness. He took 30 drops per day for a period of six months. In May, 1929, he noted a small lump the size of a pea just to the right of the anus. It increased in size and ulcerated. The lesion was

excised at Walter Reed Hospital, Washington, D. C. Pathological report, "squamous carcinoma." Wound did not heal so the patient went to the Mayo Clinic where a wider excision was made September 25, 1929. The wound was sutured and healed *per primam*. About August, 1929, there appeared numerous cutaneous nodules over the body, arms, and legs. The lesions were small, flat, encrusted and gradually enlarged. November 8, 1929, one on the right chest wall was excised at the Naval Hospital. The microscopic report was "squamous-cell epithelioma." In November, 1929, a skin specialist excised a small lesion from the right arm which microscopically was also reported to be epithelioma.

On physical examination, besides the scars of previous operations, numerous skin lesions were found all over the integument. The lesions varied from 0.5 to 1.5 centimetres in diameter. The edges were raised, crusted and grayish in appearance. These lesions included both hands. On December 6, 1929, a drop of mustard-gas solution was applied to a lesion on the chest wall, 1.5 millimetres thick and 1 centimetre in diameter; also

to another smaller lesion on the forearm. These lesions reacted typically to the application of mustard gas. (See Fig. 6.) These lesions disappeared and were replaced by thin derma. Fig. 7 shows these lesions forty-four days after the application of the solution. There has been no recurrence. The scars are pliable, well healed and painless.

CASE II.—*Epithelioma*.—

A. H. F., male, aged fifty, came to the Memorial Hospital November 30, 1929. About fifteen years earlier his physician had given him 5 drops a day of "Fowler's solution" over a long period. At this time he noted small red spots over the dorsum of both hands. Similar lesions later appeared over his body.



FIG. 5.—This shows a mustard-gas lesion of the tongue of an adult rabbit that had been treated with a surface application of one-quarter minim of mustard gas. Animal killed three days later.

In 1917 he had developed lesions over the back, abdomen, chest, hips and hands. While in France, he was seen by Darier who advised radium. Placques were applied over five lesions and they cleared up. Many more lesions developed generally over the body. No treatment seemed to improve them.

In 1925 an ulcerated lesion the size of a half dollar developed on the dorsum of the right hand. This was excised by Doctor Neal, of the Howard Kelly Hospital in Baltimore, who later skin-grafted the area. Pathological report of the tissue was "epithelioma." In 1927 an ulcerated area on the right foot was excised. In 1928 an ulcerated lesion over the right hypothenar eminence was removed. A skin graft was made but failed to take. It steadily extended. Radium plaques were applied to the lesion with no avail. Biopsy taken in October 1929, at the Walter Reed Hospital was reported "squamous cancer."

The patient had developed a large ulcerating lesion also on the dorsum of the left hand. On coming to the Memorial Hospital the lesions were numerous and widely scattered as indicated in Fig. 8. The right hand was amputated as it had ulcerated to the tendons and bone. Several lesions over the body and behind the left ear were treated

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Fig. 6.—Showing the lesions of the chest-wall and forearm three days after the application of the mustard-gas solution. The lesion and surrounding tissues are covered with vesicles. (Case I.)



Fig. 7.—Showing the appearance eleven days after that of Fig. 6. The lesion is in the repair stage. (Case I.)



by applying $\frac{1}{4}$ minim of the mustard-gas solution. It was necessary in some instances to give more than one application to destroy the lesion completely. Fig. 9 shows a wide-spread lesion behind the left ear. Fig. 10 shows this lesion during the process of destruction. Today, six months after the original treatment, the lesion is entirely gone. This is true also of those lesions which were treated by this method over the body and back. The scars are soft and to date there is no recurrence where this was applied.

CASE III.—Recurrent Neurogenic Sarcoma.—The Interstitial Injection of Mustard-Gas Solution.—H. J., male, aged forty-eight years, came to the Memorial Hospital



FIG. 8.—Showing the wide distribution of the epitheliomata and keratoses. (Case II.)

in all probability is a completely devitalized tumor, now replaced by fibrous tissue. The reaction was of a most intense nature, precluding the use of more than 3 drops at one time.

CASE IV.—Melanoma.—R. W., male, aged thirty-five, came to Memorial Hospital October 15, 1929, having a large, fungating, foul-smelling melanoma of the plantar surface of the right foot. The disease had spread widely in the subcutaneous tissue of the leg and thigh. There were also many confluent nodes in the right inguinal region. It was a hopeless case as the extent of the disease precluded an amputation of the thigh. The large foot lesion drained serum which kept dripping continuously. In an effort to reduce the size of the lesion and to prevent such loss of body fluid, applications of mustard-gas solution were made. The lesion was cauterized by these applications. There was a marked shrinking in size, a crust formed over the lesion and there was comparatively

December 3, 1929, suffering from a recurrent neurogenic sarcoma of the right thigh. During the past five years, the patient has been operated on four times unsuccessfully for a mass lying beneath the skin of the anteromesial aspect of the thigh. Chest plate is negative for metastasis to lungs. No inguinal nodes palpable. Into the recurrent mass 3 centimetres in diameter lying over the saphenous vein, 3 minims of the mustard-gas solution were injected intratumorally on March 3, 1930. One week later for a distance of 20 centimetres from the site of injection on all sides, there was intense skin redness, board-like induration, heat and tenderness. This subsided gradually, leaving an opening which drained sero-sanguineous discharge. Portions of the tumor were occasionally extruded through the small slough of skin. October 13, 1930 (eight months later), there is a thin disk-like lesion remaining which

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little loss of fluids. The patient later died of metastatic disease into the spine causing complete paralysis below the waistline.

The application in this case was of real value—reducing the size of the lesion, the odor of the lesion and the loss of body fluids.

CASE V.—Melanoma.—J. J., male, aged sixty-two, came to the Memorial Hospital January 25, 1930. On the abdominal wall, situated below and to the right of the umbilicus, is an elevated, mushroom-like tumor which is smooth, measures 2 centimetres in diameter, and is pigmented black. No regional nodes or masses palpable. A diagnosis of melanoma was made.

The lesion was treated January 28, 1930, with 8 drops of mustard-gas solution applied to the surface—4 drops were placed at the base, sides and covering the entire tumor. January 30, 1930, 4 drops were placed on the surface of the tumor. February 4, 1930, the tumor was smaller and more shriveled in appearance. Five drops of mustard-gas solution were applied to the tumor. February 6, 1930, the tumor has reduced a half in size. February 12, 1930, the tumor was widely excised going down to the anterior sheath of the rectus muscle and removing a wide area of skin and subcutaneous tissue.

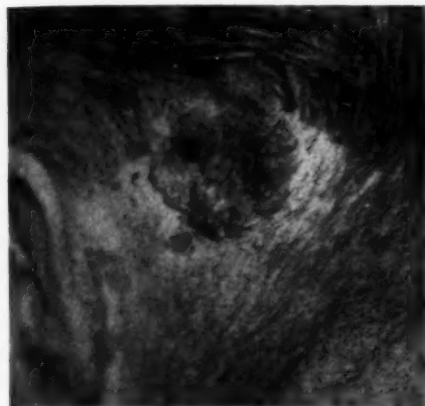


FIG. 9.—Showing the lesion of the scalp before the application of the mustard-gas solution.



FIG. 10.—Showing the lesion during the repair process.

Microscopic Examination.—Melanoma, much destruction of tumor and surrounding skin and subcutaneous tissue.

October 13, 1930, no evidence of recurrence. This case illustrates that repeated applications of this agent are possible, and that practically total destruction resulted from three applications.

CASE VI.—Neuro-fibroma.—H. G., female, aged forty-eight, came to the Memorial Hospital September 8, 1929, to receive treatment to three lesions. One was a red, indurated lesion situated in the left upper arm, apparently attached to the subcutaneous tissues. Another was located below the angle of the right scapula but more protruding and superficial. On the left heel was a projecting lesion having the appearance of a wart. The first lesion was treated by Doctor Craver with 200 millicurie minutes of the radium bulb, the second lesion had 71 millicurie minutes applied. To the third, on the heel, was applied 200 millicurie minutes. The lesions of the arm and back remained unchanged. The heel lesion disappeared.

The arm lesion was excised and proved by microscopic examination to be "chronic inflammatory tissue with slight productive fibrosis of subcutaneous tissues." On January 23, 1930, to the lesion on the back was applied $\frac{1}{4}$ minim of mustard-gas solution. This was followed by the customary ring of vesicles. In two weeks the lesion no longer protruded. April 21, 1930, the lesion of the back had disappeared. June 2, 1930, there

was a tiny scab over this site. October 1, 1930, there remains slight thickening only at the site of the former back lesion. The exact pathology of the lesion is not known.

This is undoubtedly a case where the amount applied was too small and where a second application would have been preferable.

CASE VII.—*Senile Warts*.—M. L., female, aged fifty-six, came to Memorial Hospital April 24, 1929, for treatment to several keratoses and senile warts scattered over the integument. Her skin appeared much older than her age would indicate, possibly due to a very early menopause. Many lesions were treated with X-ray and most disappeared, but a large one 2.5 centimetres in diameter in the abdominal wall persisted.

June 2, 1930, to this lesion was applied $\frac{1}{2}$ minim of 10 per cent. mustard-gas solution.

June 23, 1930, the lesion had reduced one-half in size. September 16, 1930, the lesion is entirely gone and the skin is pliable. No evidence of recurrence.

CASE VIII.—*Pigmented Nævus*.—J. DiP., male, aged twenty-eight, came to the Memorial Hospital June 2, 1930, having a pigmented nævus of the right lumbar region. It was a small purple lesion, elevated and hard.

June 3, 1930, 4 drops of mustard-gas solution were applied; within forty-eight hours there was tremendous vesiculation over the lesion and surrounding skin. September 10, 1930, the lesion is entirely gone.

CASE IX.—*Carcinoma of the Penis*.—A patient of Dr. Archie Dean. One application of mustard gas was made. One week later amputation of the penis was performed. A study of the section of the tumor showed complete destruction of the local disease by necrosis.

CASE X.—A patient of Dr. Archie Dean. This lesion was treated similarly to the above lesion except that the dose of mustard gas was slightly larger. Amputation was performed one week later. Sections of this tumor were more striking than in the first patient with penile cancer. The agent had penetrated the connective-tissue plains between bundles of fascial and muscular tissue, destroying tumor cells which had invaded these layers.

Two cases were next selected with cancer of the penis, to be treated by the mustard gas alone without amputation. These cases were managed and the treatment with the agent carried out by Dr. Russel Ferguson. Both cases were selected (a) having no penetration of the fascia by the neoplasm; (b) having no demonstrable metastases; (c) both being squamous carcinoma, Grade I, radioresistant.

CASE XI.—Patient had a lesion 2.5 by 3 by 1 centimetre thick. Frequent applications were made to the lesion of small doses of the mustard gas. The tumor has been destroyed gradually, and at present, four months after beginning treatment, there is no evidence of disease and there is good normal healing over the site of the original ulcerated tumor.

CASE XII.—The patient had a smaller growth of the penis measuring 1 by 1.5 centimetre by 6 millimetres thick. This was treated by a single large application of the mustard gas. The growth had recurred following external radiation elsewhere, three months previously. It is now five months since the treatment here in Memorial Hospital; there is no evidence of recurrence; and there is normal epithelium over the original site.

CONCLUSIONS

(a) *Animal Experiments*.—1. Tar cancers in mice may be controlled by the surface application of mustard gas in absolute alcohol. The action of this chemical produces a severe local reaction, which is slow in healing. It has been found that it is necessary to cover the entire growth completely by the solution, otherwise adjacent untreated portions of the cancer will continue to grow.

2. The removal of a tar cancer in mice by mustard gas does not prevent

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the later development of a similar tumor in an adjacent portion of the tarred area of the skin.

3. The presence of a relatively thick mass of tumor tissue on the surface of the body tends to lessen the general toxic reactions that result when mustard gas is applied to the surface of the growth. When the chemical is applied to ulcerating or bleeding areas of a surface growth the resulting toxic reactions usually result in the death of the animal.

4. Studies of the effect of mustard gas on the tongue and the inner surface of the cheek show that the action of the chemical is local and that the absorption of the liquid by the tissues is accomplished within a few seconds. There was no spreading of the action from the tongue or the cheek to other regions of the mouth in immediate contact with the treated surfaces. The doses used in the mouth did not result in destructive changes in the lungs.

5. Mustard gas on the bladder and rectal mucosa produced clear-cut local destruction of the epithelial surfaces of these organs.

(b) *Experiments on the Human.*—1. This report covers cases of skin cancer which are free from recurrence for several months following the application of mustard-gas solution.

2. In these lesions, especially squamous carcinoma, it may be necessary to make more than one application of the mustard-gas solution to effect a complete destruction of the lesion.

3. In the lesions injected intratumorally care and judgment must be exercised as the agent produces such intense inflammatory reaction that great destruction of vital parts may follow.

4. We believe that mustard-gas solution offers another agent for fighting cancer provided the lesion is localized. It is suggested that in a case of neurogenic sarcoma recurrent four times a cure may have been obtained by one interstitial injection of this agent.

ANIMAL TUMORS AS THERAPEUTIC REAGENTS

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THE recent increase of interest in the investigation of cancer, which is probably largely due to the activities of such organizations as the American Society for the Control of Cancer, has led to the announcement, largely by inexperienced investigators, of a great variety of cancer cures. Such attempts to cure cancer are usually supposed to have a physiological or pathological basis, in contradistinction to the quack variety of cure which is either a matter of absolute deception or some type of caustic substance applicable only to superficial growths. Such caustics can unquestionably cure superficial cancers, but their use has been abandoned by the profession because superior results are obtained by means of surgery and radiation.

Most of the alleged cures brought forward by the profession have therefore an apparent scientific basis. Some of them are in conception imitations of the well-known methods of bacteriology in which the injection of an antigen in animals produces an anti-serum. The serum so obtained is used in a therapeutic way. Most of the other varieties have been the employment either of autolytic products of tissues, embryonic or adult, the blood of newborn children on the admirable *nonsequitur* that as children never have cancer there must be some immune substance in the blood, neither of which assumptions is true; or, finally various products isolated from the organs of internal secretions. Such organ products may be either of normal glands or from animals which have been treated in a variety of ways, such treatment being supposed to stimulate the endocrine organs, either by making them secrete more actively or by altering them in some fashion so as to give them powers which they do not possess under normal conditions.

One of the first to attempt to obtain a cancer anti-serum was Jensen, who shared with Leo Loeb the initiation of the active experimental era of cancer investigation by showing that tumors arising spontaneously in animals of certain species could be transplanted easily. Fortunately these animals were the albino mouse and rat; hence easily handled and inexpensive to keep. Successful transplantation of the neoplasms of larger mammals has not yet been accomplished, though grafting of dog tumors has been tried since 1804. Possibly if a large number of young dogs were available, such transplantation would be successful, but even with mice and rats it is a common experience that the first inoculations in a primary tumor take in only a small per cent. often only two or three. The use of this number of dogs would be obviously limited to laboratories of large financial resources.

Jensen injected rabbits with tumor material from albino rats and treated

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tumor-bearing animals with the serum so obtained. He saw what he thought was an effective cure, but being a careful observer repeated his experiments and studied a large series of control animals, so that finally he was forced to the conclusion that the serum had little or no effect and that the apparent cures of transplanted tumors were due to spontaneous disappearance and not to the effect of the serum, as originally had been imagined.

These careful experiments apparently have never penetrated the literature of cancer, for they have been repeated over and over again by numerous investigators with negative results.

Those who have made therapeutic claims have rarely offered evidence that they knew the rate of disappearance, in untreated animals, of the tumor with which they worked.

The most important repetition of this work is due to Lumsden, whose numerous papers are summarized in the *Report* of the International Congress on Cancer in London in 1928, page 216. Lumsden found that by inoculating rabbits with mouse cancer it is possible to produce not only a general anti-mouse group of bodies which are not specific against cancer cells, but also believes he has obtained another group of antibodies toxic not only to mouse-cancer cells which were used as an antigen, but also damaging to many other varieties of malignant cells. He found also that the anti-sera made in sheep or in rats are more specific than those made in rabbits. Again, if human cancer is injected into a sheep, the sheep's serum is capable of killing cultures of mouse carcinoma or rat sarcoma, whereas the normal cells in the culture are not damaged. If such serum is injected into the leg of an animal bearing a tumor, and the circulation is slowed up by a temporary ligature, the tumor recedes, and this recession is inevitably followed by a recession of an untreated tumor of the other leg. The injection into the general circulation of such a serum is not effective, probably because of the protective action of the liver, which seizes upon foreign proteins and rapidly removes them from the general circulation. Lumsden is careful to point out that his work does not necessarily imply that the treatment would be effective on spontaneous tumors, for while he feels certain that an animal can be made to form antibodies against implanted homologous tumor cells, it cannot do so against autologous malignant cells.

Lumsden's results have been carefully controlled and are the best which have appeared on this subject of the action of an anti-cancer serum.

Attempts to produce cures, either in man or animals, by the direct inoculation of either a portion of autologous tumors or by various preparations of tumors arising in other animals, have regularly failed. The killing of tumors by trituration, radiation, or by chemicals, and the injection of material so obtained in man or animal, has not so far succeeded. The same is true of various other preparations, such as autolytic products from fetal cells, and so forth. The only fact which has been observed is that in some animal tumors—though not all—a tumor which grows and then spontaneously recedes leaves the animal immune to further inoculations. But it is

important to remember that this is not a general phenomenon, and there are some tumors in which such a sequence of events is not observable. So, too, if living cells of a great variety, blood, crushed tissue, particles of organs, and so forth, are injected into an animal, that animal becomes immune to the inoculation of a tumor, but not immune to the spontaneous appearance of a tumor; nor can such immunity against grafting be obtained in all tumors. There are highly virulent mouse and rat tumors which resist such immunity. The explanation of this phenomenon has not yet been offered. It is probable that the processes which precede the taking of the grafted tumors are very delicate and that a very small degree of immune reaction, when acting upon the implanted cells which are not yet fully nourished by necessarily newly formed capillaries, will be effective in the prevention of grafts, while it will not be effective in the destruction of an already growing tumor.

Much criticism has been made of the use of grafted tumors as a means of studying not only the biology of tumors but of testing the effect of therapeutic agents. Indeed, one prominent surgeon goes so far as to say that nothing of value has been learned in the last thirty years by the application of the experimental method to grafted tumors. It is not necessary to discuss here such an absurd statement, which is equivalent to denying any progress based upon bacterial cultures, because the cultures are not the disease, but there is an element of truth in some of the criticisms which have been made. These are based upon the enormous amount of absolutely contradictory work which has been published, and the reason for this contradiction is the lack of care on the part of the investigators in controlling their results and in generalizing from a single type of tumor. Only those who are familiar by long study with the vagaries of implanted tumors, due largely to extraneous circumstances, realize the pitfalls of the experimental methods. The use of a tumor which disappears in about 50 per cent. of the animals used would hardly be a logical basis for the announcement that a drug could cure cancer if the number of cures produced by the drug were identical with the spontaneous disappearance rate; yet such a statement has been published. Unfortunately there are very few rat tumors which do not from time to time show such extraordinary variation in their growth capacity or in the resistance of the host. Apparently such small matters as diet and the general health of the animal may play a part in such disappearance. But there are certain mouse tumors which do not disappear spontaneously, though they have been observed through many thousands of inoculations over a period of fifteen years. These tumors do not immunize against themselves and hence are just as valuable a test material as a spontaneous tumor. When such tumors are used, all the alleged cures fail. No elaborate statistical computation has to be made if this tumor has been used to decide whether the resulting disappearance is due to an interreaction between the host and the tumor, or whether it is due to an agent which is supposed to have therapeutic activities.

Using such a tumor, we can draw pretty shrewd conclusions as to the value of therapy, and it should be from a humanitarian standpoint a matter of

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compulsion that before an alleged cure is trumpeted by the newspapers, or even presented before a medical society, with the resulting inevitable disappointment and misery which ensue upon any such publicity, the alleged therapeutic substance should be tried out under the conditions outlined.

If any agent will cure, for example, 50 per cent. of the Crocker Fund mouse sarcoma 180, it will cure human cancer. Using this tumor, the colloidal lead of Blair Bell was shown not to be effective as a cure. It will therefore probably not be effective in any large per cent. of human tumors except in some which for unknown reasons seem to be easily poisoned by the lead. Nevertheless, of the many hundreds of substances tested in the Crocker Laboratory, the original Blair Bell colloidal lead is far more destructive of tumor tissue than any other substance investigated. Only a thin sheath of tumor cells remains at the periphery of the tumor after the injection of a suitable dose of colloidal lead. All the other preparations of lead used have shown themselves to be less effective in such destruction. Colloidal gold scarcely damages the tumor at all; but I am speaking not of the commercial gold which is sold about the country at an exorbitant price and which contains only a trace of gold, but of a laboratory colloid which contains large quantities of the material.

All the sera, all the adrenal cortices, all the other alleged cures or alleged treatments, have failed to influence this tumor. It is curable by surgery in the early stages before metastasis takes place. It can be cured by thrombotic agents, such as a $\frac{1}{2}$ per cent. solution of zinc chloride, provided the mouse is protected by preliminary injection of adrenalin around the tumor. It can be cured by certain of the quack caustics which destroy tissues by their corrosive action, provided metastasis has not taken place. It can be cured by sufficient doses of radium or X-ray. It therefore resembles very closely a human malignant tumor and offers a simple method of preliminary check on any therapeutic method.

Another phase of therapy of animal tumors has been valuable. The early quantitative work was begun by Mottram and Russ of the Middlesex Hospital about the same time as Wood and Prime were carrying on a long series of studies of exposures of tumors and normal tissue to radium and X-ray. The experimental proof of the large doses of X-ray or radium necessary to kill all the cells of a rapidly growing animal tumor was received by those who were practicing therapy with extreme incredulity if not absolute denial of the significance of the observations. When the experiments were repeated by some of the German workers, extraordinary pronouncements were printed, practically stating that it was impossible to cure an animal tumor with X-ray. Some of these discrepancies were due to the fact that the Germans did not take into consideration the scatter which is entirely absent when small particles are rayed, unless they are placed upon heavy wooden supports or other sources of secondary radiation. As this scatter has been found to add as high as 50 per cent. to the dose, it is easy to see that very long exposures are required under these conditions. A good summary of the subject has

recently been published by Krebs in the *Acta Radiologica* as Supplement VIII, 1929. But while these original experiments were published more than ten years ago, they have not yet received general acceptance by the practitioner. The careful measurements of X-ray and radium made possible only in the last few years have forced the conclusion that the statement made fifteen years ago that three to seven skin erythemas, depending on the tumor, are required to kill all cells of an animal tumor, are exactly true of most of the human tumors. Indeed, very interesting observations have recently been published by Martin and Quimby of their work at the Memorial Hospital in studying the end-results of the treatment of carcinoma of the mouth, in which they have shown that unless eight or ten skin erythema doses are applied to the tumor cells, a cure will not be obtained. The same observation has been made on the cervix where, owing to the anatomical independence of the uterus from other organs, it is possible to put in very heavy doses of radium; that many have been using ten to twenty erythema doses to destroy the cells of the cervical carcinomata and even under these circumstances have had to acknowledge that occasionally they have failed to have success even though the growth was restricted in its distribution.

The Regaud school have come to the same conclusion and are giving to tumors of the tongue and the metastases in the nodes equivalent to eight erythemas in ten to fifteen days. With such heroic doses, using high filtrations such as two millimetres of copper or two millimetres of zinc, they are accomplishing results which they could not achieve with lower degrees of filtration and shorter time. The explanation is probably due to the prolongation of the exposure period, and as they apparently use either a radium pack or X-ray interchangeably on this type of treatment, it is presumable that the highly filtered X-ray and the highly filtered radium are clinically equivalent. That they are biologically equivalent has been shown by Wood on tumors and Packard on drosophila eggs.

While all these results have been immensely discouraging to those who have attempted to cure cancer with radiation, they have pointed the way for real therapy as distinguished from temporary palliation. They have taught us the necessity of massive doses and the dangers of repeated divided doses of low voltage X-ray, which merely produces damage to the tissues, atrophies the blood-vessels, and, as a sufficient quantity is not administered to the deeper tissues, destruction of a large proportion of the tumor cells does not take place.

The next step will be the combination of one or more chemo-therapeutic agents with the radiation, so that the cells are damaged by the serum chemically and at the same time receive additional damage from the radiation. Whether such a combination will bring any effective control over such a multifarious disease as cancer, is a matter for future investigators to determine.

MECHANISMUS DER METHYLENBLAUATMUNG

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ZELLPHYSIOLOGISCH betrachtet unterscheiden sich Tumorzellen von den normalen Zellen durch ihre gestörte Atmung. Wird die Atmung von Körperzellen gestört, so ist die Regel, dass die Zellen zugrundegehen. Gehen die Zellen nicht zugrunde, sondern teilen sie sich trotz der Atmungsschädigung weiter, so giebt es zwei Möglichkeiten: entweder die Atmungsschädigung verschwindet wieder im Lauf der auf sie folgenden Teilungen. Dann hat man zwar ungeordnetes Wachstum (z B Granulome), aber keine Tumoren. Oder die Atmungsschädigung verschwindet nicht im Lauf der auf sie folgenden Teilungen, die Atmungsschädigung wird vererbt von Zelle zu Zelle. Dann hat man Tumoren. Dies ist keine Theorie, sondern eine Zusammenfassung der vorliegenden Stoffwechselmessungen. Es giebt im Körper höherer Tiere keine von Zellteilung zu Zellteilung persistierende Atmungsschädigung, ausser in der Zellen der Tumoren.

Bei dieser Sachlage erscheint es wichtig, Wirkungen näher zu untersuchen, mit denen man die Atmung lebender Zellen steigern kann. Ueber eine solche Wirkung und ihre chemische Erklärung sei hier kurz berichtet.

Barron und Harrop haben gefunden, dass die Atmung kernloser roter Blutzellen (Mensch, Hund, Kaninchen) auf das 10- bis 20-fache steigt, wenn man in sie eine minimale Menge Methylenblau hineinbringt. Nach Versuchen des Verfassers mit F. Kubowitz und W. Christian liegt bei der Methylenblau-Atmung eine gekoppelte Katalyse vor, bei der die Verbrennung der organischen Substanz, wie bei der Sauerstoffatmung, durch die katalytische Wirkung einer Eisenporphyrinverbindung hervorgebracht wird.

Bringt man Methylenblau in rote Blutzellen, so oxydiert das Methylenblau zweiwertiges Haemoglobineisen zu dreiwertigem Methaemoglobinoisen, während es selbst in Methylenweiss übergeht:

Methylenblau + Haemoglobin = Methylenweiss + Methaemoglobin (1).
Das so gebildete Methaemoglobin oxydiert in der Zelle Zucker oder dessen Spaltungsprodukte zu Brenztraubensäure, Kohlensäure und Wasser, unter Rückbildung von zweiwertigem Haemoglobineisen. Auf (1) folgt.

Methaemoglobin + Zucker = Haemoglobin + Oxydationsprodukte des Zuckers (2) und ausserdem bei Gegenwart von Sauerstoff.

Methylenweiss + Sauerstoff = Methylenblau (3).
sodass also eine minimale Menge Methylenblau beliebige Mengen Zucker auf dem Weg über die Haemoglobinoxidation verbrennen kann. Nach ihrem chemischen Mechanismus ist die Methylenblauatmung eine gekoppelte Katalyse: Methylenblau oxydiert das Blutfarbstoffeisen katalytisch, das Blutfarbstoffeisen oxydiert den Zucker katalytisch.

Ist dies richtig, so muss es möglich sein, die Erscheinung der Methylenblauatmung auch ohne Methylenblau hervorzurufen, indem man Methylenblau durch andere Methaemoglobinbildner ersetzt (die allerdings die Zellen nicht schädigen dürfen). Ein für unsre Zwecke geeigneter Methaemoglobinbildner ist Amylnitrit. Setzt man Amylnitrit zu roten Blutzellen, so wird das zweiwertige Haemoglobineisen in das dreiwertige Methaemoglobineisen verwandelt. Fügt man Zucker hinzu und bringt die braunen Methaemoglobinzellen in den Brutschrank, so sieht man, wie das Methaemoglobin in kurzer Zeit von dem Zucker reduziert wird. Wie bei der Methylenblauatmung entstehen als Endprodukte der Oxydation Brenztraubensäure, Kohlensäure und Wasser. Dabei wird die vorher braune Zellsuspension, wenn sie mit Luft gesättigt ist, ziegelrot (Farbe des Oxyhaemoglobins), wenn sie mit Kohlenoxyd gesättigt ist, kirschrot (Farbe des Kohlenoxydhaemoglobins). Ohne Zucker bleibt die Zellsuspension braun. Wegen der Schnelligkeit der Reaktionen und wegen der leicht erkennbaren Farbänderungen eignet sich dieser Versuch als Demonstration in der Vorlesung.

Die hier nur angedeuteten Experimente erklären die von Ehrlich vor vielen Jahren entdeckt "vitale Methylenblaureduktion." Ueberall, wo Atmung ist, findet man, wenn man den Sauerstoff abschliesst, Methylenblaureduktion. Ueberall, wo Atmung ist, hat man bei Abschluss von Sauerstoff zweiwertiges Eisen, nämlich das zweiwertige Haemeisen des Atmungsferments. Da nun zweiwertiges Haemeisen, wie die Versuche mit roten Blutzellen lehren, Methylenblau zu Methylenweiss reduziert, so müssen alle atmenden Zellen bei Abschluss von Sauerstoff Methylenblau reduzieren. Es müssen ferner bei der Methylenblauatmung dieselben Oxydationsprodukte entstehen, wie bei der Sauerstoffatmung, weil der Mechanismus der Oxydation in beiden Fällen identisch ist. In beiden Fällen ist die Oxydation der organischen Substanz eine Oxydation durch Haemeisen. Methylenblau ersetzt also nicht etwa den Katalysator der normalen Atmung, das Haemeisen, sondern es ersetzt nur den Sauerstoff. Bei der Sauerstoffatmung oxydiert der Sauerstoff das Haemeisen, bei der Methylenblauatmung oxydiert das Methylenblau das Haemeisen.

Die theoretischen Grundlagen der hier besprochenen chemischen Reaktionen findet man in den Arbeiten von Conant und Fieser sowie von Mansfield Clark.

III

REGIONAL CANCER

- DEAN LEWIS, M.D. Baltimore, Md.
Professor of Surgery, Johns Hopkins Medical School.
"Elephantiasis Nervorum."
- PIERRE MASSON, M.D. Montreal, Canada
Professor of Pathology, University of Montreal.
"Giant Neuro-Nævus of the Hairy Scalp."
- MAX CUTLER, M.D. New York, N. Y.
Formerly Director of Cancer Research, New York City Cancer Institute.
"Transillumination of the Breast."
- JOSEPH COLT BLOODGOOD, M.D. Baltimore, Md.
Clinical Professor of Surgery, Johns Hopkins Medical School.
"Border-line Breast Tumors."
- BURTON J. LEE, M.D. New York, N. Y.
Clinical Director of Memorial Hospital.
"Cystosarcoma Phyllodes Mammæ."
- BERNARD F. SCHREINER, M.D. Buffalo, N. Y.
Surgeon to the State Institute for the Study of Malignant Disease.
"The Results of Treatment of Cancer of the Breast; Based on a Study of 489 Cases, 1914-1925."
- M. LENZ, M.D. New York, N. Y.
Director of Radiology, Montefiore Hospital.
"Metastases to the Skeleton, Brain and Spinal Cord from Cancer of the Breast, and the Effect of Radiotherapy."
- JOHN M. T. FINNEY, M.D. Baltimore, Md.
Clinical Professor of Surgery, the Johns Hopkins Medical School.
"Papilloma of the Duodenum. Report of Case Diagnosed Pre-operatively."
- RAPHAEL BASTIANELLI, M.D. Rome, Italy
Professor of Surgery, University of Rome.
"Cancer of Perigastraduodenale."
- EVARTS T. GRAHAM, M.D. St. Louis, Mo.
Professor of Surgery, Washington University, School of Medicine.
"The Prevention of Carcinoma of the Gall-Bladder."
- HOWARD A. KELLY, M.D., LL.D. Baltimore, Md.
Emeritus Professor of Gynecology, Johns Hopkins Medical School.
"Electro-Surgery in Gynecology."
- BENJAMIN S. BARRINGER, M.D. New York, N. Y.
Attending Urologist to Memorial Hospital and Fifth Avenue Hospital.
"Carcinoma of the Prostate."
- HARRY C. SALTZSTEIN, M.D. Detroit, Michigan
Member American Society of Control of Cancer.
"Some Commoner Difficulties in Diagnosis and Treatment of Carcinoma of the Rectum and Colon."
- ERNEST A. CODMAN, M.D. Boston, Mass.
Former Registrar of the American Bone Sarcoma Registry of the American College of Surgeons.
"The Pathology Associated with Rupture of the Supraspinatus Tendon."
- CLAUD REGAUD, M.D. Paris, France
Director of the Radium Institute of the University of Paris.
"Une Variété Histologique D'Epithelioma Du Col De L'Uterus."

ELEPHANTIASIS NERVORUM

BY DEAN LEWIS, M.D.

OF BALTIMORE, MD.

IN THE laboratory of Surgical Pathology of the Johns Hopkins Hospital tissue may be found which has been removed from seventeen cases of multiple neurofibromatosis. In four cases the tumors developed upon a circumscribed area of distribution of a nerve. The general and localized forms are much the same histologically and can possibly be best grouped under the term elephantiasis nervorum. In 1891, Bruns analyzed forty-two cases of so-called *Rankenneurom* or plexiform neuroma which had appeared in the literature, and reported the findings in eight cases observed by himself. The fusiform or nodular strands of tissue which were imbedded in soft, succulent, interstitial tissue represented thickened and elongated nerves in a circumscribed area of the subcutaneous tissues and skin. The nodular thickening of the nerves was caused by a connective-tissue growth of the nerve sheath, the perineurium and endoneurium. With the stains then at command, no new formation of neurofibrillæ could be made out. Neurofibrillæ may be demonstrated passing through such growths, but they probably are not newly developed and cannot be regarded as taking any active part in the formation of the growths occurring on the nerves. Bruns states in his article that the origin of these tumors and their relation to other tumors developing upon nerves are of the greatest interest. He believed that they represented a form of congenital elephantiasis, if by this term may be understood a congenital anlage, predisposing to tumor-like connective tissue growths which involve the skin and subcutaneous tissues, affecting sometimes the blood-vessels; at other times the lymphatic vessels; and still at other times the nerves—elephantiasis telangiectodes—lymphangiectodes and neuromatodes. If the nerves are affected, the term elephantiasis neuromatodes might be employed. The *Rankenneurom* or plexiform neuroma should be considered as a form of congenital elephantiasis. In this type of tumor a limited part of the nerve is involved. As the result of connective tissue growth the nerve becomes thickened and elongated. These growths differ in form, only, from the multiple fibromas of the skin and nerve trunks observed in von Recklinghausen's disease. They are essentially of the same nature. The plexiform neuroma and the multiple neurofibromata are congenital. Sometimes there is a history of a hereditary tendency. They are frequently multiple and of the same histologic structure. Bruns groups, therefore, under the term elephantiasis nervorum the so-called general neurofibromatosis, plexiform neuromas, in which the tumors develop upon the circumscribed area of distribution of the nerve, and those tumors developing on the terminal distribution of cutaneous nerves—fibromata mollusca.

Five of the seventeen cases previously referred to were cases without deep nerve tumors. Eight cases had deep nerve tumors; in four cases the tumor occurring upon the deep nerves was malignant; in four cases benign. Of the four benign tumors one occurred upon a peripheral nerve, two upon cranial nerves within the skull, and one occurred upon a nerve in the spinal canal. In three instances the tumors were not general, and in still another case the lesion presented was that of a localized cutaneous neurofibromatosis.

Those cases without deep nerve tumors are not of any great interest and

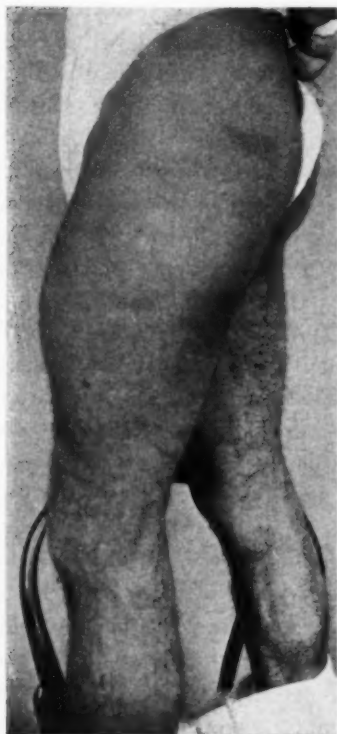


FIG. 1.—Prominence of thigh indicates position of a sarcoma developing in neurofibromatosis.



FIG. 2.—Section of tumor which rapidly recurred after partial removal of the tumor seen in Fig. 1.

will be dismissed without much discussion. The superficial tumors were in some cases scattered indiscriminately over the body. In some cases, however, there was a linear and symmetrical distribution. Frequently the tumors reached a certain size and then ceased to grow. Other tumors might appear *de novo*, or might develop from a minute nodule which had been previously discovered. In one case 118 tumors were removed at the request of the patient for cosmetic reasons.

Patients with elephantiasis nervorum seem to be especially disposed to malignant degeneration of the tumors which develop in the nerves. The predisposition to malignant degeneration seems to be more marked in the

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general than the localized form. Perhaps I have not enough cases upon which to base such a statement, but malignant changes were not observed in the localized forms.

Elephantiasis Nervorum with Deep Nerve Tumors.—CASE I.—G. B., white male, aged twenty-eight years. This patient was first admitted to the Medical Service during August, 1920. He stated that he had had lumps all over the body since early childhood. The one behind his right ear was noted by his mother when he was one year old. New lumps appeared from time to time. They frequently ceased to grow, but did not disappear. These are not painful or tender. In 1918 a tumor behind the right ear was excised, and a tumor on the left leg partially removed. The patient was again in the hospital on August 8, 1926, when a small tumor was removed from the left side of the chest. This was diagnosed as of the type occurring in von Recklinghausen's disease. Recently there has been some stiffness of the left knee and disturbance of function of the left leg. This is due to a large, pedunculated tumor which has been present for fifteen years, but which recently has grown large and hangs down over the knee.

An examination reveals numerous small tumors over the body. A large, soft, boggy mass is present in the anterior part of the left thigh, which extends from just below Poupart's ligament downward and hangs over the knee. The overlying skin has a soft, elastic texture. Palpation of the tumor suggests a fluid wave. The patella is located in this mass of tissue.

October 4, 1926, an operation was performed. A large cavity was found in the tumor which communicated with the joint. When this was opened about 800 cubic centimetres of fluid were evacuated. The tumor seemed to infiltrate the muscle. The patient returned in January, 1929. A large mass had developed over the left side of the pelvis just above Poupart's ligament. Examination revealed a large, hard mass just above Poupart's ligament which extended to the umbilicus and caused some protrusion of the abdominal wall. The tumor is stony hard in consistence and apparently extends into the pelvis. Loops of intestine seem to lie over it. The mass in the leg is much smaller than when the patient was last in the hospital.

January 19, 1929, a biopsy was performed. Part of the tumor was removed without opening the peritoneal cavity. The tumor was firm and fibrous in character. A diagnosis of spindle-cell sarcoma was made.

Since the above diagnosis was made the patient has been getting radium treatments which have so far not affected the size of the tumor.

CASE II.—E. H., white female, aged fifty years. *Diagnosis.*—Sarcoma in soft parts of left hip. Since childhood the patient has had drawing pains in the left leg and thigh. She had worn red flannels and massaged the lower extremity because of these pains. Curious pigmented spots and blotches were distributed over the trunk, abdomen and extremities. Since childhood numerous painless, slightly firm, subcutaneous nodules have been noted on the lower extremities. These have increased only slightly in size, and at the present time measure from 2 to 6 centimetres in diameter. The pains in the left leg have been more severe during the last ten years, and the difficulty in lifting and flexing the left leg and thigh has been more pronounced. Five or six years ago she noticed that the left hip seemed slightly larger than the right one. A definite enlargement has been noted for a year. The tumor was operated upon one year before admission to this hospital. It was attached to the sciatic nerve, and could not be entirely removed. Since this incomplete operation the tumor has increased rapidly in size in spite of radium treatment. The pain has been so severe that narcotics were required. Hearing is impaired in the right ear. Patient complains of numbness on the right side of face. The diagnosis of malignant degeneration of a tumor in general neurofibromatosis was made. December 11, 1922, an attempt was made to remove the large tumor in the sciatic nerve. The patient died on the day of the operation.

A pathological diagnosis of spindle-cell sarcoma with extensive necrosis and degeneration was made.

CASE III.—J. W., white female, aged thirty years. Two years before entering the hospital the patient noticed a tingling sensation in the right leg and sometimes a sharp, stabbing pain around the right knee. Six months ago she first noticed a lump in the back of the right thigh just above the knee. This gradually increased in size and the tingling and burning sensation in the leg became more severe. No motor disturbances noted. The patient states that she had observed numerous small tumors over the body for years.

Examination revealed slight fulness on the posterior surface of the right thigh just above the popliteal fossa. This fulness is caused by a hard, lobulated, egg-shaped mass 6 centimetres in length, which lies between the hamstring tendons. Pressure causes pain in the tumor and along the outer side of the calf and heel. Sensation is slightly impaired. On the left side the foot is clubbed. On the anterior surface of the trunk are numerous soft, slightly elevated tumors which measure 1 to 3 centimetres in diameter.

On January 25, the tumor, which was firmly adherent to the popliteal nerve, was excised. It is stated in the history that this tumor was so intimately connected with the external popliteal nerve that some fibres of the nerve had to be divided when the tumor was removed. The tumor was circumscribed, measuring 5 centimetres in its longest diameter; 3 centimetres across.

This patient is reported as having died November 11, 1919, of sarcoma. The diagnosis made of the tumor which was first removed was fibromyxoma.

CASE IV.—C. M., white male, aged twenty-six years, was admitted to the hospital during April, 1922. The symptoms began two years before admission. A diagnosis of static flat-foot and Morton's disease was made soon after the onset of symptoms. The pain passed up the left foot along the leg as high as the knee. He returned to the dispensary in April, 1922, complaining of pain and swelling in the left thigh. He gave the history that two years before he accidentally struck his hand against the left buttock and noted a tender spot. No tumor could be palpated. Some weeks later he noticed a small, hard nodule beneath the skin. This was about the size of the end of his finger. The lump gradually increased in size and has remained sensitive to trauma. At about the same time he noticed a swelling which was entirely distinct from the one felt posteriorly. Both tumors have increased in size.

On the anterior surface of the left thigh is a deeply located tumor which begins about 15 centimetres below the anterior superior spine and is about 18 centimetres wide and 22 centimetres long. It is not tender on pressure; is elastic, but does not pulsate. Multiple fusiform tumors are scattered over the body just beneath the skin.

Another mass, measuring 16 centimetres in each direction, begins at the left gluteal fold and extends downward on the posterior surface of the thigh. This mass is freely movable. The skin over it is normal and on palpation this mass is quite sensitive. Several chains of nodules can be palpated along the anterior and posterior surfaces of the forearms, and another chain, which extends along the internal surface of the arms into the axilla can be felt. This arrangement suggests a plexiform neuroma. Dark brown, pigmented areas varying in size from freckles to spots, measuring 6 centimetres in diameter, are scattered over the body and extremities. An operation was performed April 11, 1922, for removal of the tumor lying posteriorly. The fibres of the sciatic nerve were separated by the tumor. A line of cleavage between the tumor and nerve was found. The tumor was removed from the nerve, some of the capsule being left behind. The tumor on the anterior surface of the thigh was connected with the femoral nerve, and it was necessary to divide some of the nerve fibres running into the tumor, which was then enucleated in one mass.

The pathological diagnosis was fibromyxoma (benign) of the nerve sheath.

The following note is found on the history: "July, 1922, the patient has a recurrent

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sarcoma of the left thigh. Pathological study reveals that this tumor is very cellular and malignant."

The questionnaire was returned unanswered, so the ultimate result cannot be determined.

CASE V.—The history of the following case will be given because the specimen illustrating the structure of this tumor will be reproduced. This patient is a white man, aged twenty-one, who has tumors symmetrically distributed over the body. One tumor on the outer side of the left arm about the middle is larger than the others. Some eleven years ago he discovered by accident a mass upon the inner aspect of the right arm. Since that time numerous other small nodules have appeared over the entire body. Recently there has been considerable pain in the tumor on the outer side of the arm which has radiated over the distribution of the radial nerve. Scattered over the body are numerous well-circumscribed tumors of varying size. The greater number are about the size of a pecan. Most all are superficial. They are firm, somewhat rubbery in consistence, and in general follow the distribution of cutaneous nerve trunks. In the left arm along the course of all the radial nerve in the radial groove is a tumor mass, fusiform in shape, constricted near the middle. Pressure on the mass causes tingling over the distribution of the radial nerve. Pigmented areas are also noted in the skin. The tumor of the radial nerve was removed because of the sensation experienced when this nerve was touched or struck. It could easily be enucleated from the nerve.

The patient returned in March, 1930. A tumor was removed from the ulnar nerve on the right side. This tumor, which appeared myxomatous in places, could easily be enucleated. The tumor which had been removed previously from the radial nerve seemed more fibrous structurally.

This case is cited because the histology of the tumor removed from the ulnar nerve will be discussed later.

In the following case the tumors developed upon the nerves in one extremity. The extremity was greater in circumference and in length than the one on the opposite side. A linear distribution of the tumors could be made out. This distribution was most pronounced over the short saphenous nerve and along the posterior tibial nerve as it passed into the foot posterior to the internal malleolus.

CASE VI.—R. W., white female, aged four years. A biopsy was performed September 28, 1928. The following history was given. About sixteen months before admission to the hospital, it was noted that the left thigh and leg were larger than the right. During the sixteen months there has been a progressive, symmetrical increase in the size of the left lower extremity and hip as compared with the right. Thirteen months before admission small, tender, subcutaneous nodules appeared in the region of the head of the left fibula. There has been no pain. The patient favors the right leg somewhat. The nodules have grown slightly.

The left lower extremity and left side of the pelvis are obviously larger than the right. The extremity is symmetrically and smoothly enlarged and the tissues do not appear flabby. The hypertrophy involves all of the tissues from the gluteal muscles to the tip of the toes. There is no difference in muscle power; no limitation of motion, no spasticity or pain. There is some eversion of the left foot. Near the left knee and ankle, both medially and laterally, firm, discrete masses which seem somewhat like strands of hypertrophied muscle may be made out. These nodules appear over the distribution of the short saphenous nerve. The nodules which can be palpated posterior to the internal malleolus are located along the course of the posterior tibial nerve. No asymmetry of the body is noticed elsewhere.

DEAN LEWIS

On September 18, 1928, some of the tumors posterior to the internal malleolus were excised. In doing this some of the fibres of the posterior tibial nerve were cut. The nerve was then sutured. The appearance of the masses removed may be seen in Fig. 4.

Another instance of asymmetry associated with multiple tumors of nerves of an extremity will be given.

CASE VII.—A. C., white female, aged fourteen years. When the patient was one and a half years of age the mother noted that the right ankle and foot were larger than the left.

Shortly thereafter it was noted that the entire extremity was larger. The relative difference in size of the two extremities has increased up to the time of admission to the hospital.

The patient, a healthy girl of fourteen, has no abnormality except that of the right lower extremity. This extremity is of greater circumference than the left. It is longer and there is a deformity of the knee and ankle. As a result the patient walks with great difficulty. The weight is borne on the dorsum of a club-foot. A lobulated tumor or tumors may be palpated beneath the deep fascia. There seem to be many tumors. The cylindrical masses, one to two inches in diameter, cause a great enlarge-



FIG. 3.—Marked enlargement of the left lower extremity with increase in length associated with multiple tumors of the nerves. The situation of some of these behind the internal malleolus is indicated by the prominences.



FIG. 4.—Type of tumor masses removed from the posterior tibial nerve just above the ankle-joint.

ment of the posterior upper two-thirds of the leg and lower part of the thigh. There is distinct tenderness on deep pressure over this region. Measurements indicate that the right thigh is 4 inches larger than the left, and the right calf 3 inches larger. The right lower extremity is $5\frac{1}{2}$ inches longer than the left. The muscle power of the right leg is diminished. An X-ray examination of the bones of the right lower extremity reveals an increase in length, decrease in diameter and structural atrophy.

This patient was on the service of Doctor Willis Campbell, of Memphis, Tennessee,

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who by repeated operations removed many lobulated tumors. The extremity was decreased considerably in size. The femur was then shortened, and later the ankle was stabilized by removing the astragalus and the leg shortened by removing 1 inch of both bones. The lower epiphysis of the tibia was destroyed, but it was thought that the excessive growth in the epiphysis of the other bones would make up for this. After the operations on the soft parts and bone, the extremities were of the same length. The right leg was approximately 1 inch greater in diameter than the left. This patient was reported well on July 17, 1929. Histologically a diagnosis of neurofibromatosis was made.

The tumors which have been reported differ clinically, but are essentially of the same nature structurally. The generalized type, with tumors upon the peripheral nerves, has a marked tendency to malignant degeneration. Those cases in which one extremity has been involved have been characterized by an increase in the diameter and length of the extremity. In the latter group, pigmentation of the skin and fibromata mollusca have not been a part of the clinical picture. Neither have there been changes like those of lobulated elephantiasis which are associated with neurofibromatosis when the superficial nerves are involved.

The tumors upon deep nerves in von Recklinghausen's disease seem prone to undergo malignant degeneration. Excluding three patients who had symptoms associated with an intracranial or intraspinal growth only, sarcoma developed in four of the five cases. One of these tumors was inoperable; the other three recurred following enucleation or resection of the nerve involved. The tumors grew rapidly, early attaining a relatively large size, and recurred soon after attempt at removal. The tendency of these tumors to become malignant has been emphasized from time to time. In 1891 Garré reported seventeen cases in which sarcomas developed in tumors upon the deep nerves in von Recklinghausen's disease. Ten of these developed in nerves of the upper extremity, the median being the nerve most frequently affected. The growth usually extends along the nerve primarily affected, many nodules developing in the nerve. Cases have been noted in which secondary malignant nodules developed in the ulnar, radial or cutaneous nerves of the same side when the primary tumor was situated in the median nerve. In the transition stage between the benign neurofibroma and the sarcoma it may be difficult to state whether the tumor is benign or malignant, even by histological examination. The diagnosis of malignancy is usually not made at operation as there is nothing characteristic enough to warrant such a conclusion, although malignant degeneration of a tumor already present may be strongly suspected. The three cases in which the tumors were localized to an extremity have shown no tendency to malignant change. This is too small a group to justify any conclusion as to the frequency of malignant changes. Structurally these growths are the same as those of the diffuse forms and there is no reason why malignant changes should not occur.

Trauma and incomplete removal have, in a number of cases, been the factors which apparently predispose to malignant change. This change not infrequently occurs after incomplete removal of a tumor which has been diagnosed as benign. There is always a possibility in such cases that

malignant changes have occurred in the portion of the tumor which was not removed. In Case V, two tumors were removed, one from the radial, the other from the ulnar nerve. These were removed because of tingling and pain over the distribution of the nerve and increase in size of the tumor. Incomplete removal should be avoided and repeated trauma prevented, if possible, because of the dangers of malignant changes.

Multiple tumors occur in this disease in the nerves, meninges and central nervous system. The tumors connected with the peripheral nerves differ structurally from the single neuromas occurring in peripheral nerves.



FIG. 5.—Section through one of the tumor masses, removed from Case V showing long connective fibrils. Some of the type B neurinoma tissue is interspersed between these strands.

In earlier times when the tissue composing these growths was described as striated, composed of parallel fibres and fibrillæ, local or regional variations in the histologic picture were considered as secondary. If there was a localized nuclear richness, the tumor was regarded as a sarcoma largely because of the similarity in structure to tumors in other parts which ran a malignant course. The softening with myxomatous degeneration, followed by collections of fluid and cyst formation, was regarded as secondary changes similar to those occurring in other tumors of mesodermal origin.

Verocay was the first to recognize the mixed nature of the tissue found in neurofibromatosis and gave a description of the tissue observed by others before him who failed to grasp its significance. Antoni has shown that the type B tissue, which has a reticular structure without the palisade arrangement

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of the cells characteristic of the type *A* tissue, is always present in the tissue occurring in neurofibromatosis (neurofibromas). Many of the tumors occurring in the disease under discussion are apparently pure fibromas. In the central forms of neurofibromatosis pure neurinomatous tissue which occurs in the solitary neuromas may be found. Its occurrence accounts for the relative frequency of central changes in these cases. Penfield states that the tangled or reticular tissue which constitutes the background of all neurofibromas should be considered as a connective-tissue (and probably also a sheath of Schwann) reaction about the fibres of the nerve. Thickening of the nerve trunks, which may be generalized in these cases, is caused by just such a perineuronal hyperplasia of the connective tissue about nerve fibres. When the reaction is marked, a swelling is found on the nerve which must literally be called a tumor, but which, in a strict sense, cannot be called a neoplasm. These tumors differ considerably histologically from the solitary tumors occurring upon peripheral nerves to which the term of neurinoma was given by Verocay. These tumors have but little, if any, tendency to malignancy, as has been recently shown by Lewis and Hart. Penfield agrees with Bielschowsky and Rose that the central changes are regressive ones beginning with adult cells, and points out on the other hand that the same is true in the peripheral nerves. Thus the reactionary and neoplastic process is carried out by fibroblasts which preserve their differentiated characteristics and not by glial cells. The proliferative changes in the fibroblasts in these cases may advance to or pass into the stage of malignancy. This tendency to malignant degeneration in these cases is indicated by the frequency already referred to, in which sarcomas have developed on pre-existing benign tumors. In the growth of the neurofibroma, the reticular tissue, which is supposed by many to be a relative change, is often suppressed. The definite tendency to malignant changes in neurofibromatosis is inherent in the structural changes occurring in the neurofibromatous tissue. The occurrence of ciliated epithelium, as in the tumor described by Garré, indicates the possibility of the sheath of Schwann contributing to definite structural changes in the tumor.

These tumors differ structurally from the solitary tumors occurring in peripheral nerves which are composed of neurinomatous tissue. This is pathognomonic of a growth which has but little tendency to undergo malignant changes.

GIANT NEURO-NÆVUS OF THE HAIRY SCALP

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OF MONTREAL, CANADA

A LONG series of studies on pigmented moles has led me to believe that these tumors are formed essentially by abnormal proliferation of the ends of the tactile nerves. In a general way, this conclusion agrees with that expressed by Soldan in 1899; but it differs in certain essentials. Soldan held that nævi were neurofibromata of the tactile terminations and that, like the "neurofibromata" of the nerve trunks, they were formed by fibromatous proliferation of the connective tissue of the nerves; while I believe that nævi are not connective-tissue tumors at all. In nævi, as in the "neurofibromata" of the nerve trunks, the characteristic element is the syncytium of Schwann, the peripheral neuroglia of Nageotte, emigrated from the neural crest; but, in the nævi, the Schwann cells are partially neurotized. I shall state briefly the proofs that have led me to this conclusion.

The derma of a cellular nævus presents cells of various forms disposed in a constant order. Near the epidermis the cells are rounded, isolated or grouped in columns and more or less pigmented in the different specimens. A little deeper, the cells are more or less elongated like connective-tissue corpuscles; they anastomose with one another and are often grouped in bundles. Among these elongated or round nævus cells, it happens quite frequently that certain cell groups construct more or less typical but very characteristic Wagner-Meissner corpuscles. Careful examination shows that the rounded cells beneath the epidermis are continuous with the nævic tactile corpuscles and these with the more deeply placed elongated nævus cells; and finally that this vast syncytium is continuous with the medullated nerves of the derma. Neurofibrillary impregnations show that the nævus cells are partially occupied by neurites.

If to this group of observations we add that the nævus cells have only a superficial resemblance to connective-tissue corpuscles but that they have all the essential characteristics of Schwann cells, we arrive at the conclusion already stated that nævi are neuromas and neurinomas at one and the same time. Furthermore, the analogies of the superficial rounded cells with the cells of Merkel-Ranvier, satellites of the intra-epidermic ivy-like (*héré-diformes*) endings, those of the nævic corpuscles with Wagner-Meissner corpuscles, leads logically to the conclusion that nævi are neuroneurinomas of tactile nerves.

The specimen, the subject of this paper, was taken at autopsy from a child of three years, who died of bronchopneumonia a few hours after entering the hospital at Strasbourg. The assistant making the autopsy noted a decided elevation of the entire hairy scalp, clearly limited in front, along the sides and behind by the line of insertion of the hair. The hairs were sparse, revealing a white epidermis, everywhere smooth and flat.

NEURO-NÆVUS OF SCALP

Palpation gave an impression of soft elasticity and vague fluctuation, suggesting phlegmonous infiltration.

Incision revealed an enormous thickening of the derma and of the hypoderm, which were fused together in a perfectly white homogeneous tissue and separated from the epicranium by a thin layer of loose cellular tissue. The fibrous mass measured from 1.5 to 2 centimetres in thickness. In short, it was a generalized and almost smooth pachydermia of the entire hairy scalp. Since it was impossible to remove the whole tumor without mutilation, we were obliged to content ourselves with strips from along the line of incision. The tissue was fixed in Bouin's picro-formol and cut perpendicularly to the epidermic surface. All sections presented the same features.

HISTOLOGICAL EXAMINATION

General View.—One border of the section is formed by normal epidermis, though poor in hair follicles and sebaceous glands. The other border is a thin layer of loose

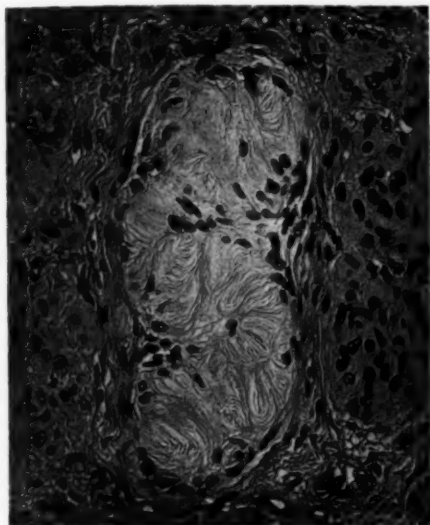


FIG. 1.—Nævic tactile corpuscle, apparently isolated in the connective tissue. In reality, this corpuscle is connected by its lower pole with the neuroid bundles. Note the characteristic laminated structure of this corpuscle, which is two or three times larger than a normal Wagner-Meissner corpuscle.

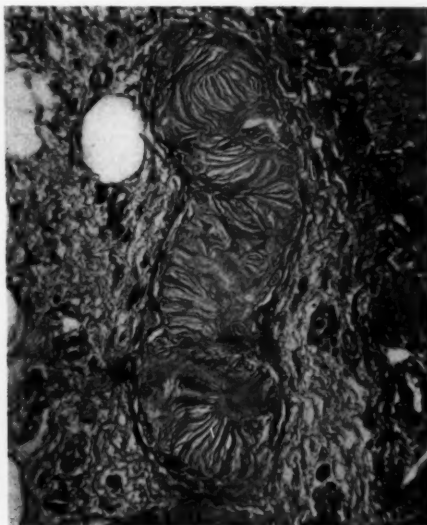


FIG. 2.—Another example of Nævic corpuscle surrounded by fibrous connective tissue. On the left are seen neuroid bundles cut almost transversely and connected by anastomoses. On the right, interlacing of cells (neuroid fibres) without precise bundle formation.

connective tissue. Between the two is the tumor tissue proper, consisting of two layers of almost equal thickness. The deeper layer, containing tiny groups of fat cells, corresponds to the hypoderm; the more superficial layer is compact and corresponds to the fibrous derma. The derma is more or less completely infiltrated as follows: Sometimes the dermal fibrous tissue is recognizable for a certain thickness, sometimes the epidermis is separated from the tumor only by the papillary layer which itself is more or less infiltrated. It is obvious that the tumor has invaded the skin from below upward. We shall study first the deeper portion of the tumor, corresponding to the hypoderm and the fibrous derma, then the superficial region beneath the epidermis.

THE DEEPER REGION

Low Power.—After staining with trichrome (iron hæmatoxylin, ponceau and aniline blue), the tumor tissue is seen to be formed of pink bundles interlacing and anastomosing in all directions and incompletely separated by dark blue bands or septa of fibrous connective tissue. These bands represent the dermal or hypodermal connective

tissue; they are traversed by voluminous arteries which often run alongside of medullated nerve fibres. Embedded in the fibrous septa and often half fusing with the pink bundles there are rounded, oval or multilobular bodies formed of folded laminae piled one on the other, obviously gigantic tactile corpuscles of the Wagner-Meissner type.

High Power.—(a) The Bundles.—At first sight, these bundles seem to be formed of elongated cells of purely but feebly acidophil protoplasm of homogeneous, glassy structure. In each of these cells there is an irregularly oval nucleus containing 2 to 3 karyosomes; each cell seems to be isolated from its fellows by a thin collagen sheath. More attentive examination shows that in reality these cells are not completely isolated but that their cytoplasm anastomose by prolongations sheathed with collagen. Each bundle, then, is formed of a multinucleated and plexiform syncytium. It has the same structure and the same significance as the *neuroid bundles* that I have described in *nævi*.

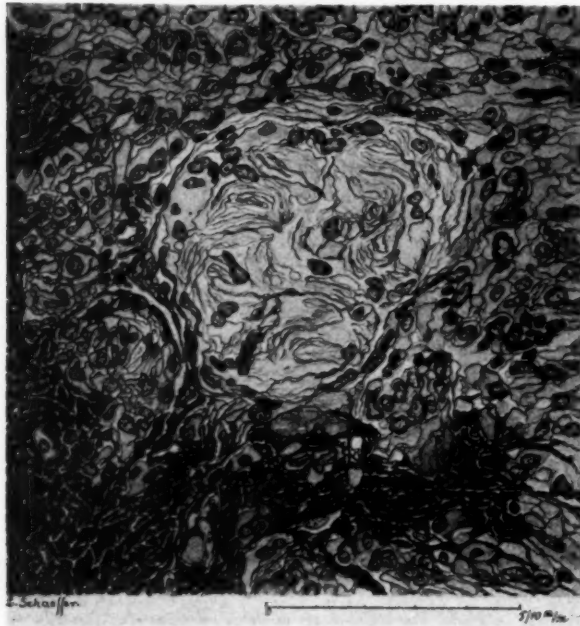


FIG. 3.—Nævic corpuscle of rounded form half-buried in a neuroid bundle of indistinct contour. On the right of this corpuscle, its constituents are seen to be continuous with the plexus formed by the cells of the neuroid bundle.

described elsewhere. This resemblance is all the more striking in that many of them become flattened and their cytoplasm is thus divided into thin, intercommunicating leaves by septa of reticulated collagen. These are typical leaflike laminae.

(b) The Nævic Corpuscles.—These laminae are rough sketches of tactile corpuscles. There are all intermediate forms between them and the gigantic tactile corpuscles illustrated in Figs. 1 and 2.

The corpuscles are always attached to the syncytium of the bundles. Sometimes they are half buried in a bundle (Fig. 3); sometimes they are distant and surrounded by connective tissue (Figs. 1 and 2) but connected with a neighboring bundle by a narrow pedicle, often laminated. It is obvious that they correspond to local differentiations of the cells of the bundles. The corpuscles never contain a nerve spiral; like the corpuscles of *nævi*, they consist solely of piled-up discs, laminated and intercommunicating, identical with those which form the supporting structure of normal Wagner-Meissner corpuscles.

If we now study the relation of these bundles to the medullated nerve fibres which

Silver impregnation by Laidlaw's method shows that the multiple collagenous sheaths of this plexus consist of a delicate network of reticulin, of which the most voluminous fibres run almost longitudinally in relation to the cell and are bound to one another by a transverse web of much more delicate fibres. This is exactly the disposition of reticulin around the medullated nerve fibres.

The border of the bundles is often well defined (Fig. 2, left); at other times indistinct (Figs. 2 and 3, right) because some of their cells escape more or less capriciously into the connective tissue. These aberrant cells may be very long, always surrounded by their sheath of reticulin; they are identical with the neuroid fibres or *nævi* that I have

NEURO-NÆVUS OF SCALP

traverse the connective tissue of the tumor and ramify there, we find the following situation. Most frequently the relations are distant; the nerves surrounded by their perineurium lie in the fibrous connective tissue separated from the bundles by a more or less thick layer of collagen fibres belonging to the derma or the hypoderm. Elsewhere, the nerves, still surrounded by their perineurium, are included in the tissue of the bundles but without continuity with them; or the tortuous nerve fibres, not surrounded by a perineurium, lose themselves among the cells of the bundle with which they seem to be continuous. This disappearance of the nerves in the bundles is not confined to any certain level but appears through the entire thickness of the deep zone. Furthermore, it does not involve all of the nerve fibres, many of which reach the superficial region of the derma, where we shall meet them presently.

By all of these characteristics, by its structure, by the tactile corpuscles to which it gives birth, by its relations with indisputable medullated nerves, the deep zone of our tumor must be considered as constituted of the Schwannian syncytium of the tactile nerves. It is a diffuse, fasciculated and plexiform neurinoma. Unfortunately the fixation of the tissue did not permit deciding if and in what measure neurites took part in its constitution.

The interesting observations of Itchikawa, then of Oertel, on the budding of nerves in the most diverse neoplasms, epitheliomas and sarcomas, and their invasion of tumor cells are well known. This phenomenon, the indisputable reality of which I have been able to confirm, by its generality lessens in great measure the importance that I formerly attributed to the presence of neurites in nævi as demonstrating their nervous nature.

The Superficial Region.—This region corresponds to the papillary layer and the upper half of the fibrous derma. Its aspect varies greatly at different points. In places the fibrous tissue is normal and free from all foreign cells; the tumor bundles have not extended above the deep region of the derma. At other points it is invaded more or less completely by the bundles, which change their aspect gradually as they approach the surface. In the neighborhood of the papillary layer, they lose little by little their coherence and the clearness of their contours. While remaining continuous, the syncytium enlarges its meshes, which become more and more conspicuous and insinuate themselves between the dermal fibres. Without any other modification, the tumor cells may thus gain the immediate vicinity of the epidermis. More often, however, when these superficial expansions of the tumor tissue reach the papillary layer, their cells lying nearest the epidermis change character gradually. Spherical or polygonal from reciprocal pressure, grouped in rounded masses or in columns, their character as epithelioid nævus cells is all the more obvious in that many of them contain melanin.

It should be noted that in the superficial region of the tumor there are no characteristic voluminous tactile corpuscles but merely the rough sketches, constituted by flattened or cylindrical neuroid fibres divided into imbricated or piled-up lamellæ by the collagen septa issuing from their sheaths. In all this region, many slender nerve filaments disappear among the tumor cells, with which they seem to be continuous.

Everywhere in the papillary layer there is a notable quantity of melanin, contained either in the fixed cells or in large macrophages ranged along the vessels. The pigment is distributed unequally; it is particularly abundant where there are masses of epithelioid nævus cells.

The epidermis presents similar pigmentary inequalities and, as in many other nævi, a few Langerhans' cells. At certain points, however, the Langerhans' cells have multiplied and accumulated (Fig. 4), forming more or less voluminous masses between the basal layer and the Malpighian cells. Nowhere do they seem to have migrated into the

derma or to have taken part in the formation of the naevus, contrary to that which, after Unna, so many observers, myself included, have seen in other naevi.

Thus constructed, our tumor possesses all of the histological features of a pigmented mole or, better, a neuro-naevus. By its extraordinary dimensions, it differs from those that I have described formerly. In this respect, it should be classed among the pachydermias of the hairy scalp first described

by Jadassohn and known as *cutis verticis gyrata* (Unna), *cutis verticis striata* (Veress), *pachydermie vorticillée* (Audry), the naevic nature of which was demonstrated by Malartic and Opin, Lenormant and Curtis. This specimen is a smooth pachydermia.

This tumor differs from ordinary naevi by the enormous development of the deep zone, which forms a vast fasciculated and plexiform neurinoma at least 1 centimetre thick, and by the gigantism of its tactile corpuscles.

It presents a further peculiarity, the inconstancy of the epithelioid cells which are found only at certain points in the superficial zone, often too distant from the epidermis to warrant an epidermal origin. This feature is of interest in showing that a naevus may be constituted in all of its fundamental characteristics without the epidermis playing any rôle whatever in its construction, all of its elements, even the superficial epithelioid cells, springing from the cutaneous nerves.

Since it is certain, in other specimens, that the Langerhans' cells migrate into the derma and are there transformed into epithelioid naevus cells and incorporated in the tactile neuroneurinoma growing up from the deeper zone, it is quite probable

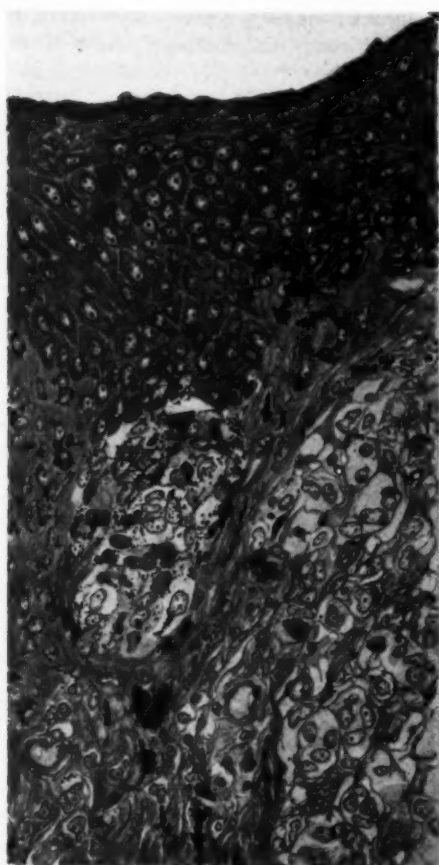


FIG. 4.—Superficial region of the neuro-naevus. Above, the epidermis, presenting a mass of Langerhans' cells which have proliferated at the tip of an epidermic ridge. All around it, the papillary layer contains fixed cells filled with melanin. On the right and below, many epithelioid naevus cells. These cells are continuous with the neuroid bundles of the deep zone, from which they seem to spring. In this specimen, none of the naevus cells seem to have migrated from the epidermis.

that the normal Langerhans' cells are not of epithelial but of nervous origin.

TRANSILLUMINATION OF THE BREAST

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TRANSILLUMINATION as a diagnostic aid in medicine has been largely confined to a very limited group of pathological conditions. Although this method has been employed for many years in the diagnosis of inflammatory conditions of the sinuses and in the differential diagnosis between cystic and solid tumors of the testis, its use in the breast before 1929 had been totally neglected. A careful review of the literature at that time failed to reveal any reports dealing directly with the use of transillumination in the differential diagnosis of breast tumors.

In June, 1929, the writer¹ reported the results of transillumination in a series of 176 breast lesions examined in the Memorial Hospital. Following this initial report the method was adopted in various American and European clinics. Since the writer's original communication, further observations have revealed some points of interest and practical importance in the use of this method. It is the purpose of this communication to relate briefly these newer observations, to state the conditions under which transillumination is an aid in the differential diagnosis of lesions in the breast and particularly to reemphasize some of the necessary precautions in the technic of examination and the interpretation of the findings.

When it is considered that a hydrocele transmits light readily and thus establishes the presence of clear fluid, it is at once obvious that a cyst of the breast containing clear fluid would transilluminate with equal facility. The importance of establishing the exact physical nature of a breast tumor is self-evident. For example, Bloodgood has demonstrated that a palpable cyst containing clear fluid is usually a benign lesion, whereas a cyst containing bloody fluid is, in the majority of instances, malignant. Sir Lenthal Cheate² and Bloodgood agree that once a cyst becomes clinically palpable it may be regarded, with rare exceptions, as benign whereas the dangerous cysts are those of microscopic dimensions.

When a tense cyst is situated deep in the breast, it may be extremely difficult to detect its cystic character. Under these circumstances a deeply situated, benign cyst is usually regarded as a solid tumor and the radical operation is performed when only a local excision is necessary. This error is especially likely to occur when a superimposed inflammation gives rise to slight adherence of the overlying skin. The clinical picture of a firm tumor associated with skin adherence often leads to a diagnosis of carcinoma and the radical operation.

The conception that the transmission of light through tissue might yield information of practical value in diagnosis was first developed among the

members of the laboratory staff of the Memorial Hospital (New York) during the routine examination of breast specimens. The marked variations in the degree of translucence in different portions of normal and pathological tissues was especially impressive. These observations suggested the possibility of establishing some points of difference between tumors of different density. The problem of testing the translucence of various breast tumors instituted at the suggestion of Ewing was pursued by Adair,³ who encountered difficulties because of the excessive heat developed by the transilluminating lamp.

It is important to appreciate that in common with other diagnostic methods, transillumination is an aid and not an absolute means of diagnosis. The method is based upon the varying translucence and opacity of different tissues. In the interpretation of the transillumination findings a knowledge of the underlying pathology of breast lesions is essential. Thorough familiarity with the gross anatomical and microscopical structure of lesions in the breast renders an interpretation of the transillumination findings more simple and leads to a more accurate judgment of the physical nature of the tumor. This information taken in conjunction with the clinical history and clinical findings enable differential diagnosis to be made with a greater degree of accuracy. With certain exceptions, transillumination alone has not enabled a differentiation between benign and malignant solid tumors nor can this accomplishment be expected. If the solid tumor is a hæmatoma this distinction is made without difficulty and the method constitutes the only non-operative means of establishing the diagnosis.

Technic.—Unless transillumination is performed in a totally dark room the result of the examination is not satisfactory. The transilluminating lamp must be a cold lamp of sufficient intensity to penetrate the tissues of the breast. It must be attached to a rheostat so that the intensity of the light can be varied conveniently by the examiner. The lamp must be so constructed as to permit the light to emanate from one point only in order that the light from this single source can be directed to the particular portion of the breast under consideration. The patient is placed in a sitting position and both breasts are examined routinely. The general scheme is to place the light directly beneath the lesion in question so that the part of the breast under consideration lies between the light and the examiner's eye. It is obvious that tumors that are attached to the chest wall are not amenable to transillumination. Under these circumstances the diagnosis is usually clear without the aid of this method. In tumors situated deeply in a thin, flat breast it may be more convenient to transilluminate from side to side.

It is necessary to emphasize that careful attention to the intensity of the light is a most important detail in the technic. The most formidable source of error is the over-illumination of small solid tumors thus establishing a false translucence. This error usually occurs when the tumor is small and especially when because of its superficial situation in a thin, flat breast the strong

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light is placed in close proximity to a small mass. Under these circumstances the light diffuses around the tumor and a shadow cannot be detected. If the lamp is held in place and the intensity of the light reduced by means of the rheostat, a shadow will be noted which is faint at first but increases as the intensity of the light is diminished. It is highly important, therefore, when examining small lesions to reduce the intensity of the light to a minimum and to interpret the faintest shadow as positive. This important detail was pointed out in the original description of the method and was subsequently reemphasized when it was learned that this source of fallacy had not been sufficiently stressed.⁴

Fat is highly translucent, consequently the large fat breasts transilluminate very satisfactorily. Dilated ducts and acini filled with epithelial debris and stagnant secretions are opaque to transillumination. Breasts in which this process is pronounced fail to transmit light readily. Breasts which are the seat of Schimmelbusch disease may fail to transmit light of the intensity usually employed.* The satisfactory transillumination of these breasts requires a light of greater intensity.

The technic of transillumination of the breast is relatively simple. The patient is examined while sitting on a revolving chair. The lamp is held against the under surface of the breast and gradually moved as different areas in the breast are inspected successively; the object being to place the particular site in question directly between the light and the examiner's eye. By means of gentle pressure on the upper surface, thus compressing the organ between the hand above and the light beneath, the degree of translucence may be increased. The tail of the breast is best transilluminated by placing the small curved lamp underneath the axillary fold, and directing the light anteriorly.

The Normal Breast.—Marked anatomical and physiological variations in normal breasts are well recognized. The appearance of the normal transilluminated breast depends upon its anatomical structure which in turn depends, to some extent, upon its physiological state.

The wide variation in the anatomical constituents of the normal breast is paralleled by corresponding differences in the degree of translucence. Fat is highly translucent; fibrous tissue is less translucent. Solid epithelial masses, fibro-epithelial masses, and epithelial debris are moderately opaque and blood is intensely opaque. Fat breasts transilluminate well regardless of their size. As the fibrous and epithelial contents of the breast increase, the degree of translucence diminishes.

A breast which is the seat of mazoplasia (chronic mastitis) is less translucent than a perfectly normal breast. The diffuse opacity is more marked before and during the menstrual periods when the hyperplasia of the duct

* The author is grateful to the General Electric Company for its aid and coöperation in developing a more intense light, and to Doctor Failla for his help in constructing a special lamp suitable for transillumination in these cases.

and acinous epithelium is most pronounced. Dilated ducts and acini filled with desquamated epithelial debris are barriers to the passage of light; consequently parts of the breast in which the hyperplastic process is most marked show corresponding relative opacities.

It is important to point out that small, flat, non-pendulous breasts closely applied against the chest wall are unsuitable for transillumination. Lesions situated in the depth of this type of breast cannot be transilluminated satis-



FIG. 1.—Appearance of the normal breast on transillumination.

factorily as it is practically impossible to place the lesion between the lamp and the examiner's eye. Superficial lesions, however, can be examined quite satisfactorily by transilluminating with a small lamp from side to side.

Cystic Tumors.—Cysts containing clear fluid are translucent. This finding renders transillumination a valuable aid in the interpretation of the physical nature of tumors in the breast in which clinical examination leaves a doubt as to the solid or cystic nature of a mass.

The absolute knowledge of the precise physical nature of a breast tumor is usually of considerable prognostic diagnostic and therapeutic importance. In many instances, clinical examination alone yields sufficient information to establish the diagnosis. That errors in differential diagnosis in this field occur with marked frequency is well known to all who have examined a considerable number of breast tumors and followed them to operation. An

TRANSILLUMINATION OF THE BREAST

early and very cellular carcinoma may present a circumscribed elastic tumor that gives many of the physical signs of a benign cyst. The true nature of the lesion is discovered only after local excision and section of the tumor. Deep-seated cysts distended with fluid fail to give fluctuation on palpation and present many of the clinical signs of carcinoma. This error is most likely to occur when the superimposition of an inflammatory process causes slight adherence of the mass to the overlying skin. Under these circumstances a simple benign cyst gives the impression of a firm solid tumor and in the presence of skin adherence, the logical diagnosis of carcinoma is made.

A knowledge of the nature of the cyst contents may be of considerable help. A clinically palpable cyst filled with clear fluid usually signifies a benign lesion. If the cyst contains blood there is strong evidence of intracystic papilloma or duct carcinoma. The opacity of blood is intense and transillumination enables a differential diagnosis between a cyst containing clear fluid and one containing blood.

Solid tumors are opaque to transillumination. The opacity

corresponds to the extent of the mass. The character of the opacity differs from that caused by the presence of blood in being much less intense. Thus transillumination enables a differential diagnosis between cysts filled with blood and solid tumors (carcinoma or fibro-adenoma).

Lactation—Galactocoele.—The lactating breast is totally opaque to transillumination. The opacity of milk is also demonstrated by the appearance of a galactocoele on transillumination. The tumor presents a sharply circumscribed and opaque shadow. Since the differential diagnosis of galactocoele



FIG. 2.—Opacity on transillumination of a solid tumor in the breast.

from other lesions in the breast is usually not difficult clinically, the practical application of this finding is of limited value. In certain cases, however, in which the clinical diagnosis is otherwise in doubt, transillumination may prove to be of considerable help in interpreting the precise nature of the lesion.

Hæmatoma.—The intense opacity of blood to transillumination has been pointed out. In view of this observation it was expected that hæmatoma of the breast following injury might present a special appearance on transillumination. The frequency with which a history of trauma is volunteered by the patient as a cause of lumps in the breast is well known. Since the breast is an organ subject to frequent and repeated trauma, the correct evaluation of such information is exceedingly difficult. The peculiar tendency of the



FIG. 3.—The appearance of a hæmatoma on transillumination. The opacity is intense, uneven and irregular in outline.

patient to attribute a lump to a specific cause, and more particularly to trauma, is well known and upon careful questioning the fact is often elicited that no relationship exists between the trauma and the tumor. On the other hand, a direct and inseparable causative relationship between trauma and tumor formation cannot be escaped in certain cases even on the closest critical analysis.

In some cases a definite trauma to the breast is soon followed by the appearance of a discrete tumor. Discoloration of the skin may or may not have been noticed by the patient. In these cases a differential diagnosis between hæmatoma and beginning carcinoma is exceedingly difficult, yet most important from a therapeutic standpoint. Frequently, slight skin adherence complicates the clinical picture and renders a diagnosis still more difficult.

TRANSILLUMINATION OF THE BREAST

Transillumination has been found to be of considerable aid in the differential diagnosis under these conditions. The opacity of a hæmatoma, being due to unabsorbed blood, is intense. The opacity varies in degree according to differences in the amount of unabsorbed blood pigments in various portions of the lesion. The edges are irregular in outline and extend into the surrounding breast tissue beyond the palpable edge of the tumor. This irregular edge is due to the extravasation of blood into the surrounding tissues.

When the lesion is examined at repeated and frequent intervals after the injury it is noted that the opacity slowly diminishes in extent and intensity and finally completely disappears. In several cases three months elapsed before the final and total disappearance of the opacity. The diminution in the extent and intensity of the opacity is accompanied by a corresponding decrease in size of the tumor.

These transillumination findings may be readily correlated with the changes known to occur in the various stages of hæmatoma formation and absorption, remembering that the opacity is due to the unabsorbed blood pigments. The opacity found in this state is unlike that seen in any other condition. It differs from that caused by an intracystic papilloma in that the latter produces a circumscribed uniform shadow with sharply defined edges. It differs from the opacity of a solid tumor such as carcinoma, in its intensity, which is never equalled by any lesion in which blood pigments do not participate.

In cases of this type, in which a differential diagnosis between hæmatoma and beginning carcinoma must be made at once, transillumination may be the means of preventing an unnecessary mastectomy. In several cases the breast was saved because of these findings. If the characteristic shadow of hæmatoma is discovered by transillumination, it is safe to withhold operation and examine the breast at frequent intervals. The slightest diminution in size of the mass accompanied by a decrease in the extent and intensity of the opacity is an indication that a hæmatoma exists and is undergoing absorption. Under observation the entire mass may disappear and an unnecessary operation is thereby avoided.

Transillumination of the Breast in the Presence of a Hæmorrhagic Discharge from the Nipple.—In order to interpret correctly the transillumination findings in this group of cases it is important to refer briefly to the pathological anatomy underlying this syndrome. Although numerous important researches have been conducted in this field it is a remarkable fact that the significance of a hæmorrhagic discharge from the nipple still remains a matter of dispute among clinicians and pathologists. Some investigators hold that a hæmorrhagic discharge from the nipple of a non-lactating breast is evidence of a benign rather than a malignant lesion and is an almost positive sign of intracanalicular papilloma. (Bloodgood,⁵ Greenough and Simmons,⁶ Deaver and McFarland,⁷ Sistrunk⁸) Miller and Lewis,⁹ on the other hand, found the same proportion of benign and malignant tumors associated with

this sign and Judd,¹⁰ in a review of one hundred cases, reached a similar conclusion.

Studies of whole sections of the mammary gland in cases of bleeding nipple have yielded important information concerning the underlying pathological process. By this method Sir Lenthal Cheate¹¹ has demonstrated that papillomata are more often multiple than is generally supposed. The uni-radicular type of papilloma, usually multiple, occurs in the deeper portions of the breast and is rarely malignant. The multi-radicular type, usually occurring singly, and situated near the ampulla of the ducts, is more likely to undergo malignant changes. In a study of a large series of breasts associated with bleeding from the nipple, Knoflach and Urban¹² found that the common lesion is a circumscribed, mostly single, occasionally multiple, papillary growth in ducts or acini, showing the histological features of a benign process. Adair,³ on the other hand, in a recent and very comprehensive study of an extensive series of cases of bleeding nipple, found that 50 per cent. of the lesions were malignant.

Careful palpation of a breast which is the seat of bleeding from the nipple sometimes reveals a tumor or a localized nodularity. In most cases, however, palpation of the breast fails to show a localized tumor and if an indefinite tumor or nodularity is discovered it may not constitute the lesion which causes the bleeding. In the absence of a localized tumor, point pressure in the region of the areola may help in localizing the lesion but this test often fails.

Owing to educational propaganda within the last few years, women now come for examination soon after a hæmorrhagic discharge from the nipple is detected. Consequently the proportion of cases in which a hæmorrhagic discharge from the nipple is unaccompanied by the presence of a palpable tumor, is constantly on the increase. Within the last few years the majority of such cases have applied for treatment so soon after observing this sign that no palpable evidence of the disease existed when the breast was first examined.

The inability to localize the lesion in cases of bleeding from the nipple is extremely embarrassing, from a therapeutic standpoint. Those who look upon this sign as of serious import, practice the removal of the entire breast. This is certainly the safest procedure but in view of the fact that the underlying lesion is often a simple benign papilloma, a removal of the entire breast may be unnecessary in many cases. Bloodgood reports two cases in which the breast was removed and small benign papillomatous cysts containing blood were found when the breasts were sectioned. Miller and Lewis⁹ state that when a serohæmorrhagic discharge occurs and no tumor is palpable, the lesion is, in all probability, a small benign intracanalicular papilloma situated deep in the substance of the breast and should be removed locally. Knoflach and Urban¹² comment on this group of cases and point out the difficulties in localizing the lesion. They state that in many cases it is not possible to locate a point at which pressure causes bleeding from the nipple even after repeated

TRANSILLUMINATION OF THE BREAST

examinations. Thus it is obvious that any procedure which enables an accurate localization of the lesion and a better conception of the distribution of the disease throughout the breast would be of considerable help in the treatment of these cases.

The intense opacity of blood has been pointed out. The most striking feature of the transillumination of the normal breast is the prominence of the blood vessels. In view of these findings it was logical to expect that an intracystic papilloma associated with bleeding would yield an opaque shadow on transillumination. This suspicion was readily confirmed when the first breast was examined by this method. It soon became evident that this simple procedure constituted an invaluable aid in the localization of the small intracystic papillomata associated with bleeding from the nipple.

An intracystic papilloma which is accompanied by a hæmorrhagic discharge from the nipple presents a discrete and well circumscribed opacity that is characterized by two features: (1) its intensity; and (2) its sharply outlined periphery. In some examples, not only has the papilloma itself been localized, but the duct filled with blood leading to the surface of the nipple, could be readily followed throughout its course.

It is important to emphasize in this connection that minute papillomata may fail to cast a shadow. It is very important, when attempting to localize these small lesions, to reduce the intensity of the light to a minimum. The most common error that is made and one that leads to a failure to localize the small lesions is over-illumination. This error is especially likely to occur when the small lesion is situated close to the surface of the breast.

If a local excision is to be performed, it is important to mark the skin directly overlying the opacity with indelible ink or with silver nitrate. This procedure must be carried out while the patient is lying in the same position in which she is to lie when the tumor is to be excised. These precautions greatly facilitate the surgical procedure. In rare cases, neither palpation nor transillumination reveals the site of the lesion. In two such examples the lesion proved to be very early duct carcinomata. No tumor could be felt on palpation and the transillumination findings were negative. Both lesions were of microscopical dimensions.

Multiple Papillomata.—Whereas in most cases a hæmorrhagic discharge from the nipple is caused by a single localized and circumscribed lesion, the underlying cause in some cases consists of a diffuse pathological process with numerous minute papillomata in dilated ducts. Although the association of multiple papillomata with a hæmorrhagic discharge from the nipple has been previously recognized, a clinical differentiation of these cases from those in which a single lesion is the causative factor has not heretofore been possible. This group of cases presents an important therapeutic problem. Knoflach and Urban¹² advise a complete mastectomy in this group as against a local excision in the other group. Their procedure consists in local excision of the suspected area, and, if the microscopic examination of the excised specimen indicates a diffuse process, a second operation is performed and the

entire breast is removed. This double procedure is necessitated by the inability to differentiate clinically between cases of single and multiple lesions. These authors report three cases in which local excision alone failed to stop the bleeding from the nipple, one case requiring a second operation. They warn against a too narrow excision because of the danger of leaving pathological tissue in the breast. Transillumination of the breast in these cases presents a striking picture consisting of multiple small opacities throughout the affected breast and sometimes also in the opposite breast. The opacities are intense, discrete, and localized. Adair³ has found transillumination a valuable aid in the diagnosis and treatment of this group of cases.

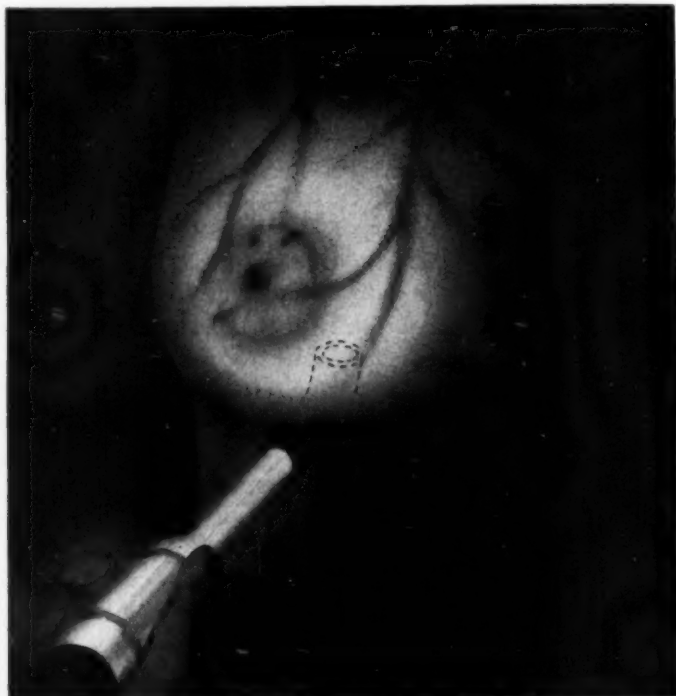


FIG. 4.—Multiple opacities seen on transillumination of a breast containing several papillomata.

It is important to emphasize that when the discharge from the nipple is not distinctly hæmorrhagic, localization by transillumination is often impossible.

SUMMARY AND CONCLUSIONS

1. Transillumination is a practical aid in the differential diagnosis of pathological conditions in the breast.
2. Different tissues display varying degrees of translucence. Fat is highly translucent. Fibrous tissue is less so. Epithelial and fibro-epithelial masses are opaque and blood is intensely opaque.
3. Transillumination enables a more accurate estimate of the physical nature of a tumor than can be gained by inspection and palpation alone. This

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information, correlated with a careful history and with the physical findings enable a more accurate judgment of the underlying pathological process than can be gained without the use of this method.

4. The normal breast presents marked variations on transillumination depending upon the relative content of fat, fibrous tissue and epithelial elements.

5. Three important technical details, to a large extent, determine the success or failure of this method. (1) The room in which the examination is performed must be totally dark. (2) When examining small lesions the intensity of the light must be reduced and the faintest shadow must be interpreted as positive. (3) In examining certain breast lesions (Schimmelpush disease) the intensity of the light must be markedly increased.

6. Solid tumors are opaque to transillumination. The opacity lacks the intensity of the shadow cast by blood. The character of the opacity in itself does not permit of a differentiation between benign and malignant tumors.

7. Cysts containing clear fluid are translucent. This finding may be of considerable aid in differentiating between carcinoma and tense, deeply seated cysts which present the clinical features of solid masses.

8. The intense opacity of blood is one of the most characteristic and important findings in the transillumination of different tissues.

9. Traumatic hæmatoma presents a specific and characteristic appearance on transillumination. The opacity is intense, uneven and irregular in outline. When the lesion is examined at repeated intervals the opacity diminishes in its extent and intensity and finally disappears as the blood pigments are absorbed. This finding may be of considerable importance in differentiating this lesion from carcinoma especially when traumatic hæmatoma is accompanied by skin adherence.

10. Intracystic and duct papilloma associated with a hæmorrhagic discharge from the nipple, present a characteristic appearance on transillumination. The opacity is intense, uniform and sharply circumscribed.

11. Transillumination is especially helpful in cases presenting a hæmorrhagic discharge from the nipple in which no tumor can be palpated in the underlying breast. In this group of cases transillumination may constitute the only available method of localizing the lesion and indicating the site for surgical removal.

12. A hæmorrhagic discharge from the nipple may be associated with a single papilloma or with multiple papillomata. Multiple papillomata (with the exception of microscopical lesions) present multiple opacities. Transillumination is therefore of considerable aid in determining the extent of the disease in the underlying breast and constitutes the only non-operative means of differentiating between single or multiple lesions. This determination is of special importance from a therapeutic standpoint in indicating the extent of the surgical procedure.

13. The practical importance of differentiating between single and multiple papillomata is emphasized by those examples in which the local removal

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of a duct papilloma has been followed by further bleeding from the nipple. Subsequent transillumination in these cases has revealed the fact that only one of numerous papillomata had been removed.

14. Transillumination is a simple procedure and a valuable aid in the interpretation of pathological conditions in the mammary gland. Its use is recommended in the routine examination of the breast.

ACKNOWLEDGMENTS

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BORDER-LINE BREAST TUMORS*

By JOSEPH COLT BLOODGOOD, M.D.

OF BALTIMORE, MD.

FROM THE SURGICAL PATHOLOGICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY AND HOSPITAL

THIS term seems to have been employed to define a lesion of the breast difficult to diagnose either clinically, or from its gross appearance, or from repeated microscopic studies, by a number of pathologists. In the great majority of cases the first diagnosis by the majority of the examiners has been malignant, yet the follow-up demonstrated that the lesion was benign.

These border-line tumors can be classified first into four main groups: (1) Clinically malignant, microscopically benign. (2) Gross picture malignant, microscopic picture benign. (3) Gross picture benign, microscopic picture malignant. (4) The largest group. Here, in the first instance, the first microscopic diagnosis was malignant. When the section is submitted to a number of pathologists, the majority favor the diagnosis of malignancy, but subsequent events and restudy all prove that the lesion is benign.

These border-line tumors of the breast were very rare between 1890 and 1900, because the majority of women with lumps in the breasts delayed one year or more. In this period the majority of examples of chronic cystic mastitis spontaneously disappeared, as did some examples of galactoceles, chronic lactation mastitis, and traumatic mastitis. Malignant tumors assumed not only the clinical picture of malignancy, but the positive microscopic characteristics of fully developed carcinoma of various types. In each decade, as the duration of the lump observed by the patient grows less, the relative frequency of the border-line tumor increases. But there are other factors, and Velpeau called attention to this in the second edition of his book on tumors of the breast. In the first edition all the diagnoses by Velpeau were based upon the clinical picture and the gross appearance. The microscope was employed more and more frequently after the publication of the first edition. In the second edition of his book this great French surgical pathologist stated that the microscope has been of little or no value to him, because the pathologist looking through the microscope diagnosed cancer when Velpeau was confident, from his vast clinical and gross experience, that the lesion was not cancer; and diagnosed benign when he was certain that the lesion was malignant. Velpeau did not live to learn the value of cellular pathology as discovered by Virchow, not to know how to explain the different interpretations between his own and this pioneer group of microscopic pathologists. More than sixty years later Welch, in making a tour of the United States, observed the same differences of opinion between the surgeon of large experience and training in the clinical and naked-eye diagnosis of tumors, and the young and inexperienced pathologists but recently called upon to diagnose

with the microscope material fresh from the operating room, either from immediate frozen sections or later permanent sections. (Professor William H. Welch, of the Pathological Department of Johns Hopkins University, confirmed Velpeau's statement made in about 1850.) The pathologist was usually incorrect. But when a pathologist of Welch's experience in the microscopic diagnosis of tumors and a surgeon of an equal experience, as William S. Halsted, conferred on a breast tumor, the clinical and naked-eye diagnosis of Halsted usually agreed with the microscopic diagnosis of Welch. Our records show that in every clinic, when the material from the operating room was sent to the pathological department and this department was not in the hands of specially trained pathologists, there was a great difference of opinion between the diagnosis of the operator and the microscopic diagnosis of the pathological department. This factor, therefore, influences the relative number of border-line cases.

I shall describe here a typical border-line case of breast tumor which was reported in Halsted's first article on the results of his operation for cancer of the breast in 1895, as cancer of the breast cured by operation. We are now convinced that this case was a chronic lactation mastitis abscess. The patient is living and free from disease today.

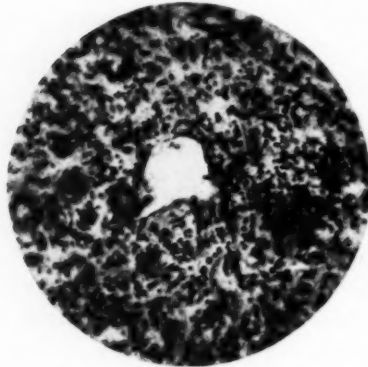


FIG. 1.—Case I. Pathol. No. 228. Section of wall of chronic lactation mastitis abscess. Diagnosed cancer in 1894. Complete operation. The patient is well, no recurrence today. See text page 236.

visible. I took the history, made the examination and assisted Dr. J. M. T. Finney at the operation.

Neither Doctor Finney nor myself at that time had had much experience with tumors of the breast. We both thought it was an abscess. In cutting down upon it to drain it we passed through normal skin and fat; then a zone of breast tissue from which milk flowed, and then a zone of breast tissue that looked different from the first zone and from the surface of which no milk exuded; then came a very thin zone like granulation tissue. The material filling the cavity did not resemble pyogenic pus, still called laudable pus in those days; it was very much thinner, resembling the thinnest kind of skimmed milk. It is quite possible it was milk and not pus. But no examinations were made, unfortunately, either chemical, bacteriologic or microscopic, of this fluid. On the other hand, it did not have the appearance of the so-called cold tubercular abscess. The character of the fluid made such an impression upon us that that Doctor Finney excised the wall of this cavity and closed the wound. Within a few days Doctor Welch examined the sections (Fig. 1) and was inclined to the diagnosis of adenocarcinoma in a lactating breast. Doctor Halsted agreed with this microscopic diagnosis and performed the complete operation for cancer. The glands in the axilla were not involved. Some three

CASE I.—Pathol. No. 228. (Fig. 1.) Date, 1894. In brief, this patient entered Johns Hopkins Hospital with a tumor of the right breast of a few weeks' duration. She was nursing a child of four months of age, from both breasts. Milk was coming from both nipples. There were none of the symptoms of acute abscess. There was no fever. On palpation, the tumor fluctuated. It was a tumor that occupied more than a hemisphere. It was

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years later a nodule like a skin metastasis developed on the arm. This was excised and found to be microscopically a fibroma. The patient had a number of children after this operation; nursed them without difficulty. She was followed for more than twenty-five years. This section was one of a number which I submitted in 1915 to a group of the most experienced and trained pathologists in this country. At that date the majority diagnosed cancer or "suspicious of cancer," or adenocarcinoma.

This is the best example of a border-line breast tumor, and allows us to give the evidence which justifies the conclusion that the microscopic diagnosis in the original was incorrect, and that this patient's breast could have been saved. Today, properly trained surgical pathologists would be able to recognize at the biopsy at exploratory incision, the distinct benignancy of the lesion, because clinically and even in the gross, the picture was unusual. In the first place, cancer cysts during lactation are possible. The history of the cancer cyst would undoubtedly be identical with this chronic lactation abscess

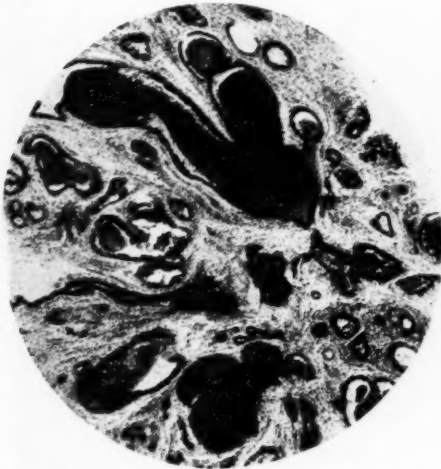


FIG. 2.—Case II. Pathol. No. 1734. Non-encapsulated cystic adenoma. Largely solid large-duct adenoma. Diagnosed cancer at Johns Hopkins in 1897. The patient lived sixteen years without recurrence. See text page 242.

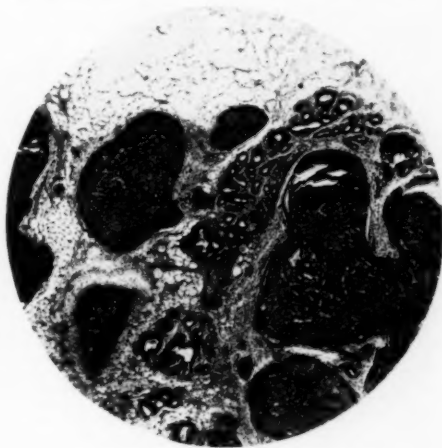


FIG. 3.—Case III. Pathol. No. 26650. Section from wall of blue-domed cyst; large, solid duct-adenoma resembling Fig. 2. Diagnosed by Bloodgood at St. Agnes Hospital, benign. Cyst removed. No recurrence in 1930. See text page 243.

or galactocoele. Both would be slowly growing, more or less painless tumors. Both would give fluctuation on palpation. In both instances there would necessarily be no change in the production of milk. Up to the present time, in my experience, the contents of a cancer cyst have either been bloody, or thick, grumous material. On one occasion it was smoky. Never have we recorded pus of the pyogenic or tubercular type, or milk-like contents. In one instance the contents of the cancer cyst has been smoky, and the operator made the diagnosis of a benign cyst and neglected the check of a frozen section. But the section of every cancer cyst recorded in the laboratory is typical of cancer and entirely different from the section of Pathol. No. 228. (Fig. 1.)

As a positive proof that Pathol. No. 228 is chronic inflammation in a lactating breast and not cancer, we have sections from a few cases of typical, clinically, lactation mastitis abscess. The surgeon in the operating room

incised the abscess and for the first time excised a piece of its wall, because there had just been introduced in his hospital a pathological department for the microscopic study of tissues removed in the operating room. He sent this tissue to the laboratory not because he wished it diagnosed, but because he wanted to obey the new rule of the hospital. To his surprise, in a few days he was informed that it was a cancer cyst, that the sections of the wall of this abscess showed undoubted cancer. As these operators were older surgeons of accumulated clinical experience in naked-eye diagnosis, they refused to accept this diagnosis and submitted the sections to a number of more experienced microscopic pathologists. They finally accepted the diagnosis of the minority group, of benign chronic lactation mastitis. These patients have been followed for years. None have developed malignancy in this or the other breast. In the past ten years no such example of an

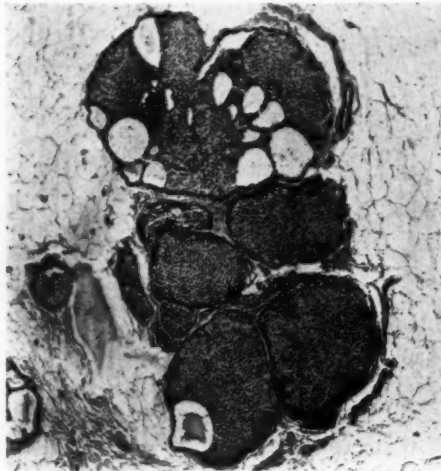


FIG. 4.—Case IV. Pathol. No. 42770. Section of non-encapsulated solid and cystic area of breast. (Doctor Cullen's case.) This area suggests benign solid adenoma and papillary cystadenoma. For more suspicious areas in the same case, see Figs. 5 and 6.



FIG. 5.—Case IV. Pathol. No. 42770. Low-power photomicrograph from solid area near Fig. 4. Suggests cancer. For high-power see Fig. 6.

abscess in a lactating breast has been diagnosed clinically or in the gross, or from a section, to be malignant. I am inclined to think that this group, in which there is a definite abscess in the chronic lactation mastitis, will give no further trouble. Nevertheless, we must teach this to our students, surgeons must bear it in mind, and pathologists assuming the responsibility of frozen-section diagnosis in the operating room must remember that in the past some experienced pathologists have made the mistake of seeing cancer in the wall of an abscess in a lactating breast. As these abscesses are becoming very rare, because we now know how to instruct the nursing mother to keep the nipple clean and free from infection, one may appear suddenly in any clinic, the operator may not know that an abscess in a tumor of the breast excludes cancer, and the pathologist may not have seen the remarkable epithelial changes in lactating breasts the seat of inflammation, acute or chronic.

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Chronic Lactation Mastitis Without Pus Formation, with the Gross and Microscopic Appearance of Cancer.—My associate, Dr. L. Clarence Cohn, will soon publish his recent studies of this group. He finds twenty examples in more than 75 per cent. of which the benign inflammatory tumor has been diagnosed cancer either because, clinically, there was retraction of the nipple or dimpling of the skin, or because it had the naked-eye appearance of cancer at exploration, or because the frozen or the permanent section was difficult to distinguish from cancer. These cases are found in the records from the earliest years to the most recent months. If the sections of these twenty tumors are studied, you will find a microscopic picture much more difficult to differentiate from cancer than the sections of the fully developed abscess wall. In spite of the fact that these inflammatory lesions of the lactating breast are growing relatively less frequent, we should teach our students and the operating surgeons and the pathologists throughout the country the importance of this group and the necessity of preparation for this diagnosis. I shall refer constantly to this point. When the incidence of cancer dropped from 80 per cent. to 17 per cent. in the entire group, and the actual proportion of malignant tumors at operation has fallen from 80 to 50 per cent., the necessity of microscopic diagnosis from frozen sections increases, and the number of tumors difficult to recognize even

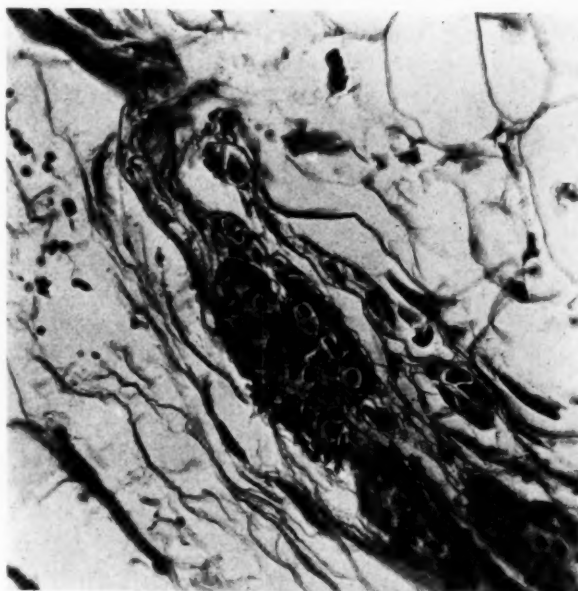


FIG. 6.—Case IV. Pathol. No. 42770. High-power area shown in Fig. 5. See text pages 247 and 248.

with the microscope increases. Every pathologist responsible for the frozen-section diagnosis in the operating room should constantly restudy sections of chronic lactation mastitis which have been verified as benign and all his other border-line tumors. The object of this paper is to bring this about.

Chronic lactation mastitis, like tubercular mastitis, and even traumatic mastitis, begins as an area of induration in some part of the breast. The size varies with the duration of the lesion; it is usually a single lesion and not bilateral. The area does not palpate at all differently from an area of scirrhous carcinoma, and there is a type of cancer of the breast that, clinically, is practically identical with mastitis. Therefore the differential diagnosis must be made at biopsy.

After writing up to this point and having before me the great mass of material of this group of border-line tumors, I find it impossible within the space assigned to me to cover the ground in the systematic manner I hoped to do. This must be left to a later monograph.

I am, therefore, taking the liberty of making this paper an introduction to the monograph. The entire staff of the Surgical Pathological Laboratory

have taken up the subject of breast tumors, and I hope this investigation will be finished, so that the most important conclusions can be summarized in the final word on border-line tumors. At the present moment I have the evidence to show that family physicians, surgeons and pathologists throughout this country, in every locality in which women are learning the correct facts in regard to breast lesions, are encountering more difficulty in the increasing number of patients who seek an examination for pain, discharge from the nipple, slight irritation of the nipple, and an indefinite lump. When the incidence of cancer is 17 per cent. and the operative group of definite tumors 35 per cent., of which more than one-half prove to be benign, and the group



FIG. 7.—Case V. Pathol. No. 42546. Photograph of gross specimen showing cystic and solid areas in a non-encapsulated palpable tumor in the breast, clinically benign. For photomicrographs of this see Figs. 8, 9 and 10.

which should not be operated upon 65 per cent. or more, the difficulties of distinguishing the benign condition for which operation is not indicated reach their height.

The second and perhaps greater dilemma is when this early tumor is explored. Definite benign lesions, instead of being 20 per cent. as they were twenty-five years ago, have increased to 50 per cent., and there is an increasing

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number of non-encapsulated tumors of various types that are difficult to distinguish from cancer even in the frozen section.

In examining the breast, we run a greater risk of overlooking malignant disease in its earliest and most curable stage. At the operation we have to decide so frequently between the danger of an incomplete operation for cancer and the unnecessary mutilation of removal of the breast for innocent lesions.

What is the evidence to justify the conclusion that the majority of these border-line tumors are benign even when the major opinion of the pathologists to whom the sections have been referred is that it is malignant? If we take the border-line tumors recorded in every group, whether benign or malignant, and place them together, we will observe that the only evidence of cancer is an occasional cancer in the one breast left behind, or in the breast from which the border-line tumor has been removed, and the per cent. of such instances is not more than the risk of cancer incurred by any woman of



FIG. 8.—Case V. Pathol. No. 42546. Benign cystic-adenomatous area near the wall of the cyst shown in Fig. 7.

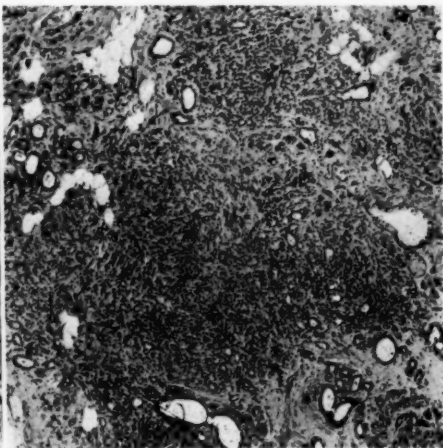


FIG. 9.—Case V. Pathol. No. 42546. Low-power solid area some distance from the cyst shown in Fig. 7, having gross appearance of cancer. See Fig. 10.

equal age over the same period of time. In none of the border-line tumors have the glands shown metastasis. In 1915, when the border-line tumors were separated from the malignant group, the per cent. of five-year cures after the complete operation for cancer in which the axillary glands, microscopically, showed no metastasis, dropped from 85 per cent. to 70 per cent.

This border-line group has always exaggerated the operative cures of cancer of the breast, and this is encouraging many surgeons in recent years to use radiation of the breast after biopsy.

The border-line tumors have given the evidence that it is not dangerous to excise a breast tumor, refer it to a pathologist for microscopic diagnosis, and then, some weeks or months later, to perform the complete operation for cancer.

It seems best now to give a few specially selected cases with illustrations,

with few exceptions, including the microscopic pictures. Only those in which the interval after operation is five years or more will be included.

CASE II.—(Fig. 2.) Observed in 1897. Pathol. No. 1734. In 1897 Doctor Halsted explored this distinctly palpable tumor in a woman aged forty-six, in which the small tumor beneath the right nipple had been present two years. There were no clinical signs of cancer. At the exploration the tumor was a non-encapsulated area containing a few cysts, a few dilated ducts from which could be expressed milk and brownish fluid, although there had been no discharge from the nipple. It is to be remembered that Halsted was a remarkable surgical pathologist. The tumor did not impress him as cancer, and a frozen section which was rarely made at that date was interpreted as benign. Later, after a careful study of the permanent sections, the diagnosis of adenocarcinoma was made and the complete operation was performed. This patient was followed for sixteen years to the age of sixty-two, and the letter addressed to the patient was returned marked "lost." Her physician wrote to me that he had lost track of the patient.

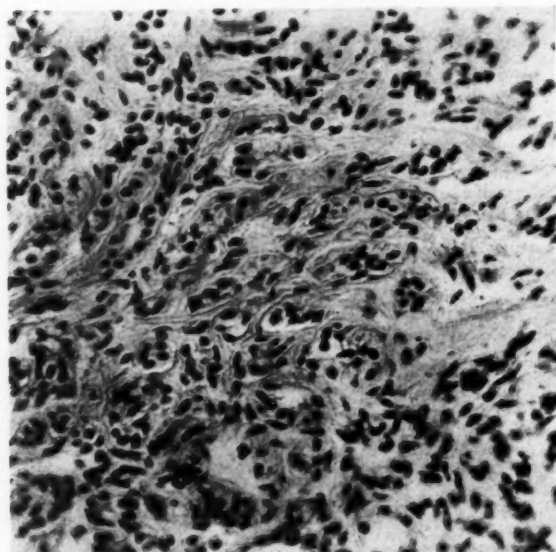


FIG. 10.—Case V. Pathol. No. 42546. High-power of area shown in Fig. 9, interpreted by the operator, Doctor Cohn, as cancer. Complete operation performed. Glands not involved. Pathologists disagree.

This observation was almost unique among the group of tumors in Halsted's clinic previous to 1900. Remember, the tumor had been present two years and was still clinically benign, which is always, even today, evidence in favor of benignancy. Between 1897 and 1921, twenty-four years, we recorded in the laboratory eighteen examples of non-encapsulated cystic adenoma similar to this case illustrated in Fig. 2. All of them

were ultimately subjected to the complete operation for cancer. In none of the cases were the glands involved; not one has died of cancer. I have reported them in the *Archives of Surgery* in November, 1921. When the section shown in Fig. 1 was submitted to pathologists in many cities in 1915, in over 60 per cent. the diagnosis was *adenocarcinoma*, and all advised the complete operation for cancer. In spite of this there is not a single example in our laboratory of a tumor of the breast in which the glands were involved, or one in which the patient has ultimately died of cancer, with a microscopic appearance resembling Pathol. No. 1734.* (Fig. 2.) As this section is given out in the examinations students find great difficulty in distinguishing it from cancer of the comedo-adenocarcinoma type. It is our best example,

* Fig. 60, page 503, in the *Archives of Surgery*, loc. cit.

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during these forty years, of a border-line tumor. The more familiar one is with the varying microscopic pictures of chronic cystic mastitis, the less difficult it is to recognize malignancy. But this picture, which is not unlike that seen in a lactating adenoma, is rare in any example of chronic cystic mastitis. It is not a common finding in the breast tissue surrounding a blue-domed cyst. (See Fig. 3, Pathol. 26650.)

CASE III.—(Fig. 3.)

Observed in 1920. Pathol. No. 26650. This photomicrograph of an area of chronic cystic mastitis is taken from the wall of a blue-domed cyst removed in 1920, ten years ago. The patient has had no recurrence in either breast since then, in spite of the fact that there is every evidence that the tissue pictured in Fig. 3 was in the remaining breast. When I examined this patient a few days before the operation, she had accidentally felt a lump four days before. Her attention was called to it when she struck her breast. Palpation of both breasts showed no evidence of chronic cystic mastitis. The breasts were not shotty, nor lumpy. There was no other tumor in this right breast nor in the other breast. It belonged to the group of a definite single tumor in one breast. The tumor was spherical, the size of a silver dollar, in the middle zone of the upper hemisphere, extending a little below the nipple. It was freely movable and fluctuated. It was diagnosed a cyst. The woman was un-

married, aged fifty, and still menstruating. If this patient were examined today and the breast transilluminated, we would have seen no shadow and we could have made a pretty positive diagnosis of a benign tumor, because no tumor of that size, if solid, would transilluminate clear, and no cyst containing blood or thick, grumous material, would transilluminate clear. When I explored the tumor I exposed a typical blue-domed cyst beneath the subcutaneous fat. When opened it contained slightly cloudy fluid; the wall was smooth and thin. In excising it, the breast looked normal. We could not recognize, with the naked eye, what the microscope showed in Fig. 3. The



FIG. 11.—See text page 248. Case VI. Pathol. No. 43014. Photograph of gross section of breast tumor clinically malignant. Operation complete for cancer. Note the thin-walled cyst to the left and the thick-walled to the right. For sections see Figs. 12 and 13.

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breast was largely fibrous and fatty. There was a second blue-domed cyst no larger than the end of the finger. In cutting out some of the breast tissue containing the two cysts, we exposed no dilated ducts as we cut through the breast tissue beneath the nipple, nor could we express from the normal ducts any material. On the gross



FIG. 12.—Case VI. Pathol. No. 43014. Low-power photomicrograph of thin-walled cyst shown in Fig. 11. Diagnosed (Bloodgood) benign.

pathology alone, nothing more was done, although the woman was fifty and unmarried. The microscopic study revealed that the cyst had no epithelial lining, but in the zone of breast there was evidence of fully developed chronic cystic mastitis in which these large, solid duct adenomas shown in Fig. 3 predominated.

This section has also been shown to a number of pathologists. In recent years the number who agree to its benignancy is increasing, but there is still a large minority who would advise at least the removal of the breast from such a frozen section.



FIG. 13.—Case VI. Pathol. No. 43014. Low-power photomicrograph of thick-walled cyst shown in Fig. 11. Diagnosed (Bloodgood) benign. (Thirty-eight pathologists diagnosed it malignant, thirteen benign.) See text page 248.

In 1921, when I studied 210 cases of single and multiple blue-domed cysts, there were, in less than 10 per cent. of the cases, microscopic pictures similar to that shown in Fig. 3.*

Among these 210 cases of blue-domed cysts, only in a very few was the

* Pathol. No. 26650, illustrated in the *Archives of Surgery* on page 502, Fig. 59.

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complete operation performed because of frozen sections made at the time of the operation. When the breast was completely removed on exploring the blue-domed cyst, it was because the operator was of the opinion that the removal of the breast protected this patient from cancer. Statistical studies show that chronic cystic mastitis is practically always a bilateral condition, although the clinical evidence at the time of the first examination showed that it was present in one breast only. To be logical, therefore, one should remove both breasts. Or, again, the operator removed the breast to save the patient from a second operation for a new cyst. I have followed more than one hundred patients from whom we have removed a blue-domed cyst from one breast. None have developed cancer. It is now more than thirty years since the first case was observed. Less than 10 per cent. have had second operations because of the appearance of a new blue-domed cyst, but in the majority of cases the new cyst has appeared in the breast not previously involved. So that removal of the breast when one explores a blue-domed cyst is not logical—one should remove both breasts. The conclusions I made in the *Archives of Surgery* for November, 1921, on 210 cases is true today, nine years later, during which period we have had an almost equal number of new cases; and, in addition, when the blue-domed cyst is clinically a multiple tumor, we rarely operate at all or we explore one tumor to make the diagnosis positive. In recent articles since 1921 I have given further evidence to justify non-interference when there are multiple tumors of the cystic type in one or both breasts, that there is no indication to remove the breast when one finds at exploration one or more blue-domed cysts. But it is a good plan to make frozen sections of the wall so as to become familiar with the varying microscopic pictures. One, however, runs a greater risk, if frozen sections are made of the wall of a blue-domed cyst, of finding pictures which will influence one to be suspicious of cancer and lead one to the radical operation for cancer.

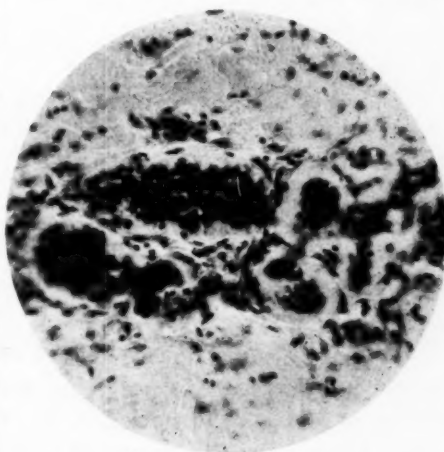


FIG. 14.—Case VII. Pathol. No. 25517. See text page 248. High-power of thick-walled cyst, similar to that shown in Figs. 11 and 13. Excised from breast seven years ago. No recurrence since. Pathologists differ as to malignancy.

Cancer and Chronic Cystic Mastitis.—In 1906* I made a report on the type of chronic cystic mastitis which was even then known in the literature as Schimmelbusch's or Reclus' disease. These two authorities had published before 1900. None of us had many cases. As far as I can make out, Velpeau and Billroth, Paget and Warren, and other pathologists of the period before 1890 had either not seen, or had overlooked this type of chronic cystic mastitis in which the single or multiple larger blue-domed cysts are rarely present.

* *Surgery, Gynecology and Obstetrics*, vol. iii, page 721, December, 1906.

These three contributions represented the beginning of intensive microscopic studies of lesions of the breast, because the modern surgery of the breast began in 1890.

There is ample evidence to prove that the conclusions of Schimmelbusch and Reclus that this diffuse, non-encapsulated, cystic adenoma or papillary cystadenoma of the breast was pre-cancerous, or associated with cancer in 50 per cent. of the cases, was due to the fact that it was difficult to differentiate in these early years between certain types of carcinoma and chronic cystic mastitis. It was repeating Velpeau's experience, who found that the young and not as yet experienced pathologists were making a microscopic diagnosis of cancer in lesions which he knew, from his vast clinical experience, were not cancer. I made the same mistake in 1906. Every case reported there either as malignant or suspicious of cancer proved, on further study, not to be cancer. The first case of Schimmelbusch's disease observed in Johns Hopkins Hospital was operated on by Halsted for cancer in 1892, clearly described in the gross and microscopic picture by Welch, but the glands were not involved and the patient is living today, thirty-eight years after operation. I described this lesion clinically and the gross and microscopic appearance in 1899. The case was identical with that described by Welch seven years before. I removed the breast, because everywhere I found these minute cysts filled with fluid or granular material, dilated ducts filled with pastille material. In spite of the conservative operation, the patient lived ten years and during this time had disappearing tumors in the remaining breast, and slight discharge from the nipple, but refused to return for operation.

In 1901 Doctor Finney removed the left breast with a typical example of diffuse Schimmelbusch's or Reclus' disease. The painting of the specimen by Horn* is the best illustration in the literature up to date. An area in this breast was at first diagnosed adenocarcinoma and was used as an argument in favor of a close relationship between this variety of chronic cystic mastitis and cancer in my paper in 1906. But this patient lived nineteen years without recurrence. One other case, reported at that time, diagnosed cancer, in which the breast was first removed followed by the complete operation for cancer after the microscopic study, lived seventeen years.

Our studies of chronic cystic mastitis and its possible relation to cancer have continued since the publication in the *Archives of Surgery* in 1921, and at the present time confirm the statements made there. Doctors Copeland and Geschickter, in the Surgical Pathological Laboratory, with the aid of the Garvan Chemical Foundation, and the Bloodgood Research Fund, are making a restudy of the entire breast material, and up to the present have found no evidence to retract any statement previously made in the literature by me since 1921. There is no doubt that, microscopically, various stages of chronic cystic mastitis, encapsulated and non-encapsulated cystic adenoma, old fibroadenoma, rapidly growing intracanalicular myxoma, all forms of tubercular and pyogenic mastitis, and changes in the breast after recent injury, must be

* *Archives of Surgery*, loc. cit., page 468, Fig. 23.

BORDER-LINE BREAST TUMORS

looked upon as border-line breast lesions, because many well-trained pathologists, when confronted with the microscopic picture either in frozen sections in the operating room, or later in permanent sections, are inclined to the diagnosis of malignancy and advise at least the removal of the breast. In 1915 I submitted a large number of such cases to pathologists in a number of cities, and in not a single instance was there a uniform diagnosis, and on the whole, the majority favored the conclusion that the breast lesion was microscopically cancer or suspicious of cancer and advised the removal of the breast, or the complete operation for cancer. All these patients on whom the pathologists disagreed in 1915, fifteen years ago, are either living today with no evidence of cancer, or have died in the interval of other causes without evidence of cancer.

Fortunately the delay in finishing this paper allows me to review briefly the recent pathological gathering in the Surgical Pathological Laboratory of the Johns Hopkins Hospital.

During two days of morning and afternoon sessions, over fifty surgical pathologists interested in frozen sections in the operating room reviewed sections of eleven breast lesions. In our opinion ten were benign and one was malignant. However, on every case, except a distinctly benign adenoma of the breast, there was disagreement. When we compare the results in 1930 with those in 1915, we can make this statement: In 1915 the majority diagnosed malignant; in 1913 the majority diagnosed benign.

Illustrative Cases.—CASE I.—Pathol. No. 228. (Fig. 1.) Wall of a chronic lactation mastitis abscess diagnosed at Johns Hopkins in 1894 carcinoma. At the pathological conference in 1915, the majority favored carcinoma. In 1930 the minority favored carcinoma. Living today, no recurrence.

CASE II.—Pathol. No. 1734. (Fig. 2.) Diagnosis at Johns Hopkins in 1897, adenocarcinoma. First removal of non-encapsulated area of cystic adenoma. Permanent sections diagnosed adenocarcinoma. Complete operation—no metastasis to glands. Patient lived free from recurrence fifteen years. Majority diagnosis in 1915, malignant; in 1930, benign.

CASE III.—Pathol. No. 26650. (Fig. 3.) (See page 237.) This section is from the wall of a blue-domed cyst which I removed in 1920, ten years ago. This section was found later in the laboratory and was diagnosed benign. Remember only the cyst and a zone of breast were excised. At the present date (1930) the patient is well and both breasts are normal. In these ten years this section has been shown to many pathologists. The majority diagnosed it malignant.

It was not submitted to the group in 1930 as we did not have enough tissue to make fifty sections.

Those interested in border-line tumors are referred to my article in the *Archives of Surgery* for 1921 which contains a number of microscopic illustrations, the majority of which have been diagnosed malignant by a varying per cent. of pathologists. But in the ten years since that article was written none of these patients have exhibited any signs of cancer, whether the operation was excision of the tumor, or the breast, or the complete operation for cancer.

Illustrative Cases Studied by Fifty or More Pathologists at the Meeting in the Surgical Pathological Laboratory in June, 1930.—CASE IV.—Pathol. No. 42770. (Figs.

4, 5 and 6.) The actual sections were examined at the same time by the visiting pathologists in June, 1930. Twenty-two voted benign, twenty-five malignant. This patient was operated upon by my colleague, Dr. Thomas S. Cullen, at the Church Home and Infirmary Hospital. The adult patient had a single tumor, clinically benign. When explored, it was a non-encapsulated area in the breast containing solid areas and of a gross appearance not suggesting scirrhous carcinoma. As the frozen section was interpreted differently by Doctor Cullen and his associates, the tumor only was removed and the sections referred to me that day. The area shown in Fig. 4 is the type of solid adenoma or papillary cystadenoma, non-malignant. The majority of the tumor had this picture. In another area cysts predominated. Fig. 5 is a low-power and Fig. 6 a high-power photomicrograph of solid areas which in my opinion should be interpreted as malignant. All of the workers in the Surgical Pathological Laboratory agreed with this. Doctor Cullen performed the complete operation for cancer. Careful examination of the glands in the axilla showed no metastasis. Some of the pathologists made these statements: The tumor is benign, remove the tumor only. The nomenclature of the benign tumors varied—duct adenoma, benign cystadenoma; benign cyst adenoma with chronic mastitis. The majority of those who diagnosed the lesion benign advised the removal of the tumor only; two, the removal of the breast. Among those who diagnosed malignancy, all who advised operation advised the complete operation. One diagnosis was suspicious of malignancy, and the advice was to remove the tumor and carefully watch the patient.

In the discussion, I am convinced, everyone looked upon this case as very difficult to diagnose. I was surprised that so many—twenty-two out of twenty-five—concluded that the tumor was benign and suggested that the tumor only be removed.

CASE V.—Pathol. No. 42546. (Figs. 7, 8, 9 and 10.) In this case my associate, Dr. L. Clarence Cohn, explored the tumor because it was clinically distinctly benign. When he removed it (Fig. 7) there was a small blue-domed cyst surrounded by a few other minute cysts. A short distance from the larger cyst there was a zone of breast that impressed him as suspicious of malignancy. Fig. 8 is a frozen section from the cystic area and shows no evidence of malignancy. Fig. 9 is a low-power, and Fig. 10 a high-power photomicrograph of the solid area of breast tissue which Doctor Cohn, and the surgical pathologist at St. Agnes Hospital, interpreted as malignant and performed at once the complete operation for cancer.

These sections should be compared with Figs. 5 and 6.

The vote on this case of Doctor Cohn's was twenty-two benign and twenty-five malignant.

It is my opinion that in Doctor Cullen's and Doctor Cohn's cases it was safer to do the complete operation for cancer, but the chances are that these patients will live, and we will never know whether the lesion was benign or malignant. But as yet, until we get a differential stain, it is safer for the patient, when in doubt, to perform the complete operation for cancer.

CASE VI.—Pathol. No. 43014. (Figs. 11, 12, 13 and 14.) This case is of great interest. The tumor palpated like two or more nodules of different sizes, each feeling like a cyst, and the breast tissue around these nodules suggested malignancy. The entire mass was freely movable in the middle zone of the breast, and when moved in certain directions, the skin over it dimpled. There was, however, no change in the nipple. On transillumination there was a dark area distinctly smaller than the palpable mass. The dark area excluded the conclusion of multiple blue-domed cysts with thin walls. As the patient was past fifty and of a very nervous disposition, I decided to do the complete operation without exploration. Doctors Stewart and Cohn, at the examination in the office, and the internes at St. Agnes Hospital agreed with me that we should class this nodule as clinically malignant. Fig. 11 is a photograph of what we found when we bisected the breast in the region of the nodule. The mass to the left is a typical, smooth,

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thin-walled, blue-domed cyst surrounded by breast tissue similar to that pictured in the middle photograph. This breast tissue had no evidence of malignancy. The second, smaller tumor was a thick-walled cyst, with clear contents, smooth lining which undoubtedly produced the dark area on transillumination. There is nothing in the wall of either cyst or the breast tissue to suggest malignancy. Fig. 12 is a section from the thin-walled cyst, and Fig. 13 from the thick-walled cyst. Fig. 14 is the high-power taken from the wall of another thick-walled cyst, and presents an accurate picture of the histology in the thick-walled cyst, Fig. 13. All of us in the Surgical Pathological Laboratory looked upon this cyst, even the thick-walled one, as benign. The cyst shown in Fig. 14 was a thick-walled cyst removed seven years ago, and the breast saved. There has been no trouble since. In spite of this, thirty-eight of the pathological group voted it malignant, and thirteen benign. That is, more voted for malignancy than in Case V.

CONCLUSIONS

There is no question that the number of border-line breast lesions is on the increase, and that the most expert pathologists today disagree when sections are submitted to them and all have equal opportunities to make the diagnosis. There may be an improvement in 1930 over 1915 but it is not sufficient to solve the problem. The surgical pathological laboratories connected with standard hospitals should be given more financial support, so they may be able to join in the search for a differential stain and give more time to meeting their colleagues in the group study of border-line lesions.

I hope shortly to publish, with full illustrations, the border-line tumors of the breast which we have collected now in the past forty years.

GIANT INTRACANALICULAR MYXOMA OF THE BREAST
THE SO-CALLED CYSTOSARCOMA PHYLLODES MAMMÆ OF JOHANNES MÜLLER
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FROM THE MEMORIAL HOSPITAL OF NEW YORK CITY

IN 1838 Johannes Müller collected several specimens of an unusual mammary tumor characterized chiefly by its large bulk, rapid growth following years of dormant quiescence, benign nature and peculiar gross and microscopic features. He considered this tumor as a neoplastic entity, and gave it the name *cystosarcoma phyllodes*.

Cystosarcoma phyllodes mammæ was an uncommon tumor even one hundred years ago. It is much less frequent now because the precursory fibroadenomas of the breast are recognized and removed and therefore the physician today does not see so many neglected advanced cases of mammary tumor. During the last twelve years at the Memorial Hospital the Breast Department has had the opportunity of studying four of these unusual tumors. A thorough perusal of medical literature covering the last century has furnished us with a total of 105 additional case reports; the present study, therefore, is based on an analysis of over 100 of these uncommon tumors.

This tumor is not peculiar to the human species as Bertolet reported the occurrence of a large tumor of one year's duration which was situated in the lower left iliac mammary gland of a nulliparous greyhound with cystic degeneration of the ovaries. In this instance the tumor was composed of multiple cysts which were almost completely filled by firm, fleshlike proliferations projecting from the cyst walls and which resembled sarcoma in its histological structure.

The tumor which Johannes Müller termed "*cystosarcoma phyllodes*" has been designated by at least twenty-five synonyms. It has been known also as "*cystosarcoma papillare*," "*cystosarcoma arborescens*," and "*cystosarcoma polyposum intracanaliculare*." Sir Astley Cooper in 1829 included these neoplasms in his group of mammary tumors classified as "cellular hydatids." Sir James Paget called them "glandular proliferous cysts," and Thomas Hodgkin spoke of them as "composite cystoids." Caesar Hawkins labeled them "tuberous cystic tumors of the breast." Schuh, in 1860, included them as a variety of "gelatinous cystosarcoma." Sir Benjamin Brodie in 1846 gave them the appellation of "sero-cystic sarcoma." Virchow in 1863 used the designation "*intracanalicular myxoma*"; Dietrich—"fibroadenoma intracanaliculare fibromatosum"; Leser in 1888, and Noetzel in 1893—"fibrocystadenoma intracanaliculare." Ziegler in 1889 used three different terms, namely, "*cystofibroma papillare*," "*sarcome rameux*" and "*intracanalicular myxoma*." Haeckel in 1894 diagnosed such a tumor as "*cystoma papilliferum*"

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mammæ." Beneke considered this tumor as an "adenoma pseudosarcomatodes"; Kreibitz likewise stressed the point that these cystosarcomas are really "pseudosarcomas." De Quervain in 1908 and Theile in 1909 called the benign tumor of this variety "fibroadenoma phyllodes" and changed the name to "fibrosarcoma phyllodes" in those instances where in the connective tissue stroma proved to be malignant. Frangenheim in 1930 also designated this tumor as "fibrosarcoma phyllodes." Wohlsecker diagnosed such a tumor as "fibromyxoma intracanalicular obliterans" because of the tendency of the connective tissue to obliterate the cysts or ducts. Bunkert used the descriptive term "fibroadenoma intracanalicular sarcomatodes xanthomatodes." Wilms adjudged this tumor to be a congenital variety of "adenomyxoma" whereas Coenen considered it as one of the "mutation" tumors. Ewing explained the etymology of the term "cystosarcoma phyllodes" as applied to tumors showing a branching system of more or less parallel cysts recalling the veins of a leaf.

Inasmuch as the neoplasm is usually not malignant the word "sarcoma" cannot be justifiably employed. We have retained the name "cystosarcoma phyllodes" because its usage for a hundred years has inseparably associated it with this tumor. In modern terminology a suitable descriptive term would be "giant intracanalicular myxoma of the breast."

Gross Pathologic Anatomy.—Sir Astley Cooper reported several cases of hydatid disease of the breast but all were not cystosarcoma phyllodes. His original description of hydatid disease (second type) corresponds to cystosarcoma phyllodes:

"The breast was enlarged and in the greater part hardened by the effusion of fibrine (coagulable lymph) in lobes into the cellular tissue; but in several parts it contained bags of serum and formed fluctuating cysts of various sizes. In each of these cells there hung a cluster of swellings like polypi, supported by a small stalk; and the little pendulous projections appeared to float in the fluid which had been produced around them in the different cysts.

"If one opens the clefts one finds communicating cysts, from which one can lift out large or conical and smooth or anastomosing and warty or villous excrescences, which somewhere adhere with a narrow or broad pedicle to the wall and continuously emerge with the connective tissue. (Virchow.)

"The dendritic intrusions into the cyst may occur at one point only, at several points, or, lastly, at all points simultaneously. In the last case, they converge, coalesce and eventually fill the entire cyst determining thus its aggregate structure. (Müller.)"

It is evident that Müller and Virchow as well as other early writers encountered much later stages of these neoplasms than are now commonly seen. Grossly the tumor tends to fall apart because of the enormous clefts and polypoid masses. On hemisection of such a tumor the intracystic contents are frequently packed so tightly that when the polyps are lifted out of the cyst they cannot be replaced. These polypoid projections may be described as cone-shaped, nodular, sessile, papillary, cauliflower, warty, arborescent, lamellar, teat-like, fingerlike or mushroom. These intracystic polypoid masses have been referred to as "papillary elephantiasis." Virchow, Orth

and Ribbert compared this tumor to a cabbage because of its frequent laminations; on section, layer after layer of flattened lamellæ can be removed. The polyps are visible to the naked eye, sometimes projecting from broad pedicles into the cysts with dendritic fimbriated extremities resembling a cock's comb. On pressure the polyps mutually flatten each other, which so distorts them that they become tortuous. Some of the polypi are flat and arranged like the leaves of a book. The polypi may become adherent to the opposite wall.

The masses may fill the clefts so well as to simulate a solid tumor. On cut section some areas appear solid like sarcoma and microscopically may be pseudosarcomatous. The anastomotic clefts appear as sinuities; these clefts are the old dislocated cavities of the ducts. Such lacunar slits in the tumor substance are supposed to be diagnostic of a benign neoplasm. The cystosarcoma phyllodes may be multilocular; the cysts are often confluent due to rupture of intervening septa.

Only a thin layer of straw-colored fluid may exist between the vegetations and the cyst wall. In other instances the secretion is mucous, gelatinous, oily or resembles old extravasated blood; at times the fluid is granular due to its content of keratinized flakes. The liquid is a secretion of the epithelium of the cysts, modified by long residence in the cysts; leucocytes are frequently present.

The stroma is commonly myxomatous, and seems loose and gelatinous. It may be smooth, striated, glistening, yellowish-white, gray or reddish-gray and telangiectatic. Occasionally hæmorrhages occur from the delicate blood-vessels in the tissue stroma. The capsule of the tumor may be highly vascular, thin and transparent. The tumor does not invade the adjacent breast tissue and thereby lacks the destructive ability of malignant neoplasms. The neighboring breast tissue frequently contains enlarged, dilated ducts, presumably caused by pressure. In the same or opposite breast other fibroadenomas may be seen in various transitional stages of gelatinous metamorphosis.

Pathologic Histology.—The giant intracanalicular myxoma, in common with the intracanalicular fibroadenoma, derives its stroma from the subepithelial connective tissue (mantle tissue) that exists between the epithelial cells and the elastica. When such tumors are studied it is realized that the bulky stroma is not simply an increase of connective tissue but has characteristic qualitative changes as well. It is a heteroplastic type of interstitial connective tissue proliferation. The myxomatous character of the stroma is the most constant feature in cystosarcoma phyllodes. When the metamorphosis occurs with replacement of the connective tissue by myxomatous tissue, then the tumor increases rapidly in size. This is an expansive rather than an infiltrative growth. Only certain lobules of the tumor become myxomatous. These myxomatous changes are more pronounced within the polyps than in other interstitial tissues of the tumor. Under the microscope

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these regions have the appearance of an interlacing meshwork of star-shaped cells and fibres.

The tumor cells are often radially arranged around the blood-vessels. This perivascular distribution is also seen in sarcoma. The spindle cells of the stroma tend to run parallel to the elongated clefts. The firm portions of the stroma are composed of fusiform cells with bizarre nuclei, which are narrow and rod-like, resembling smooth muscle nuclei. The variability of the size of the stroma cells and nuclei resembles sarcomatous tissue. However, mitoses are rare in cystosarcoma and true atypical cells are lacking. Jungst asserted that this periglandular metaplastic tissue was degenerative because he found the nuclei of the cells to be bare.

Bulky necrosis is never common, as occurs in true sarcoma. The blood-vessels of the stroma are delicate and embryonal; perivascular infiltration of lymphocytes and plasma-cells may be seen; many of the blood-vessels are thrombosed. Cholesterin crystals are sometimes seen between the tumor cells. Giant foreign body cells with multipolar kinesis engulf these cholesterol crystals. Some of the giant cells contain intracellular, doubly refractive fat which has been attributed to abnormal metabolism. Just as xanthomatous changes are frequent in degenerating breasts, so they are often seen accompanying inflammatory changes in these tumors. Hyalin changes occur diffusely, thereby decreasing the vascularity of the tumor. Hyalin metamorphosis affects particularly the polypoid tissue and the individual polypi decrease in size in this hyalin degeneration because of lessened oedema. The hyalin may become delimited in the centre of the polyps to form definite hyalin beads. Russell bodies are products of hyalin degeneration and are occasionally seen in these tumor cells. Calcareous deposits and pigment accumulation may occur in the stroma of the tumor.

The ducts of the tumor are so dilated and tortuous that no one microscopical section can ever show the entire course of one duct. The ducts become tortuous because of the connective-tissue invaginations. The ducts are the dividing tracts of the connective tissue. These very narrow ducts may grow into pseudosarcomatous structure; however, they do not form true acini. In no place is there ever any independence of the stroma proliferation from the ducts.

Not all of the polypi are covered with epithelium as some have become denuded by pressure or irritation. The majority of these giant intracanalicular myxomas have clefts lined by cylindrical or cuboidal epithelium. This cuboidal or columnar epithelium of the clefts may undergo metaplasia to form pavement epithelium, even true epithelial pearls, indicating a functional stability.

Genesis.—Mention should be made of the close relationship existing between terminal ducts, alveoli and their enveloping stroma. For instance, the stroma surrounding the terminal ducts and alveoli in the normal breast is relatively cellular and nonfibrous, whereas around the larger excretory

ducts the stroma is dense and fibrous.. It seems, therefore, that the connective tissue shares in the functional activity of the terminal ducts and alveoli. In the development of intracanalicular fibroadenoma and in giant intracanalicular myxoma, a controversy arose concerning which tissue was primarily at fault, the epithelium or the connective-tissue stroma.

Kurn, Leser, Von Saar, Schimmelbusch and Beneke believed that these tumors have their primary anlagen from the epithelium of the glands and that the changes in the connective tissue are secondary. On the contrary, Langhans, Klotz, Berka, Sasse and Virchow considered the important factors in the histology to be marked proliferation of the pericanalicular connective tissue, with secondary passive increase of epithelium. Haeckel maintains that the ducts dilate first with a consequent invagination by connective tissue. Harpeck ascribes the formation of these intracanalicular tumors to an enlargement of the excretory and milk ducts along their longitudinal ridges. Ziegler considers the cystic formation as merely the product of the connective tissue proliferation, whereas Mornard and Masson mention the possibility of origin in galactoceles. Beneke claims that this tumor owes its development to a blastomatosis of epithelium which may occur at any time in life, and the type or degree of stimulation which this epithelium is supposed to communicate to the connective tissue is unknown, but it seems to be delimited somewhat (although irregularly) to the stroma about the walls of the ducts.

In many lactating and resting breasts there is a metaplasia of the periductal and periacinar tissue into myxomatous tissue. When the duct dilates this myxomatous tissue presumably pushes the epithelium inward by an invagination and becomes papillary by budding. Later the cystic dilation may be so great as to surround almost the entire projection forming a cyst. (Jungst.)

Age.—The giant intracanalicular myxomas of the breast usually develop from preëxisting intracanalicular fibroadenomas. Intracanalicular fibroadenomas occur in the breasts of women who are generally older than those in whom occur the pubertal fibroadenomas which develop from the pericanalicular and periacinous connective tissue. The average age of the 109 patients with cystosarcoma phyllodes was 44.6 years; single women averaged 45.3 years of age. The average age of 151 patients at the Memorial Hospital with fibroadenomas of the breast was 35 years; single women were 12 years younger than the married women who had this particular tumor. The average known duration of cystosarcoma phyllodes in this series was 6.7 years; therefore, when this figure is subtracted from 44.6, the average age of the patients, we obtained 37.8 years, which is the estimated average age when the tumor first appeared. This age of onset is not significantly greater than the normal incidence for mammary fibroadenomas. Sometimes this tumor originates shortly after the onset of puberty. For comparison it is of interest to note that the average age of 2663 patients with glandular

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carcinoma of the breast was 51 years and of eighteen patients with true sarcoma of the breast the average age was 47 years.

Sex.—Wülfung has maintained that no typical case of cystosarcoma phyllodes of the male breast has ever been reported, whereas Helmuth said that this tumor has occurred a few times in the male breast. Three of the 109 patients reported in this series were males, constituting an incidence of less than 3 per cent. of all cases.

Trauma.—The influence of trauma was mentioned in thirty-one case reports. Of these, eighteen patients stated that no trauma had been experienced, whereas thirteen other subjects gave definite histories of injury to the involved breast. These occurrences seemed authentic as the histories state that the tumors began to grow within certain definite periods after the dates of injury. However, there is no evidence to prove that a small precursory and undetected fibroadenoma did not exist prior to these traumas. In several instances the neoplasms appeared to exhibit an increased rate of growth, presumably due to stimulation by trauma.

Etiological Influence of Lactation and Pregnancy.—Finsterer concluded from his study of eighteen cases that cystosarcoma could be expected to develop in breasts which have reached the climax of physiologic function by repeated births and lactations. Helmuth, on the contrary, observed that they usually appear in the breasts of unmarried and childless women. It is our opinion that repeated births and lactations are the most frequent stimuli to the metamorphosis of fibroadenoma into cystosarcoma phyllodes. It is generally well known that the ordinary fibroadenoma participates in the hypertrophy which the breast undergoes during pregnancy and lactation. Moreover, the histories of these patients state definitely that the tumor acquired a marked growth impetus during pregnancy, lactation and menopause. Physiologists have long known that whenever there is functional proliferation of epithelium in the sexual cycle such as in the breast and uterus, there is a corresponding activity often expressed in mitosis in the stroma adjacent to the epithelium. In a similar manner the stroma of the intracanalicular fibroadenoma participates in the stimulation by pregnancy and lactation.

In ninety-one instances the marital state of patients in this series was given; fifteen only (16½ per cent.) were single. In thirty-eight reports the number of children was stated; nine had one child, eight had two, six had three, one had four, two had five, five had six, two had seven, two had eight, and three had ten children. On analysis we find that the average mother in this group had four children. Several of the cases illustrate the significance of these factors. One patient, a para two, and another, a para six, had never nursed. A third patient nursed her children from her normal breast but never from the breast in which the tumor developed because of deficient secretion. Another woman, a para six, nursed her children on the left breast only, the tumor developing later in the right breast. One

patient, a para six, observed that with each pregnancy the tumor would increase in size, but would remain quiescent during the non-pregnant intervals; she never nursed from the breast containing the tumor because of a retracted nipple, although this breast lactated at the completion of each pregnancy. In another instance the tumor became swollen with each menstrual period. Two patients volunteered the information that lactation stimulated the growth of the tumor. Another woman was pregnant at the time the tumor was extirpated. Still another had only one child, nursed this child and later served as a wet nurse for two other children. In a thirty-

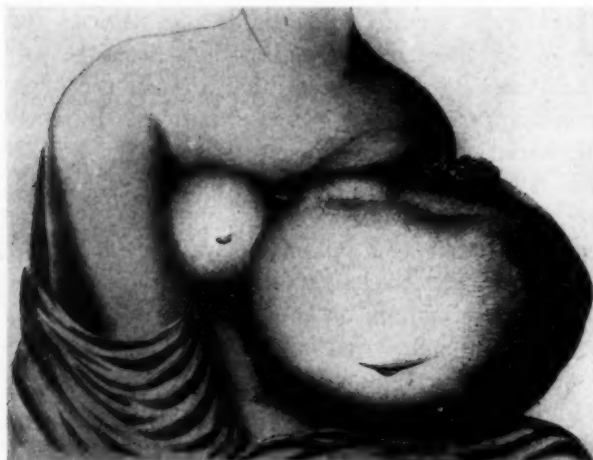


FIG. 1.—Case report by von Graefe (1838). The patient was a Russian woman, thirty-nine years of age. She had nursed her five children without lactational difficulties. After her last childbirth, a small nodule the size of a filbert (fibro-adenoma?) was felt in the right breast. This nodule never increased in size. In 1836, a new tumor appeared in the left breast and grew slowly until 1838, when it exhibited an increased impetus of growth. It ruptured spontaneously and twelve hours later a large cauliflower vegetation prolapsed through the ruptured skin. This enormous tumor covered the entire chest, displaced the right breast and a local mastectomy was done without anesthesia. While an assistant supported the breast, two surgeons with three knives amputated the breast by three slashes in less than thirty seconds. Immediate hæmostasis was obtained by compressing nine large severed vessels between the fingers. The breast and its content of tumor weighed twenty-two pounds and eight ounces. A cure was effected.



FIG. 2.—Case report by Helmuth (1871). The patient was a woman, aged sixty-eight years, who first observed a small tumor in her right breast twenty years previously. This tumor gradually increased in size until it extended from the clavicle to below the waist and from the sternum beyond the axilla to the scapular line. The integument over the tumor was tense and bluish; the tumor mass was nodular, circumscribed and fluctuant. Treatment consisted entirely of injection of carbolic acid. The patient died several months later.

year-old woman menstruation ceased spontaneously; whereupon an arrested inactive fibroadenoma grew with great rapidity. A thirty-nine-year-old woman, para five, noticed the appearance of a tumor immediately after her last childbirth, which was followed by a sudden and permanent amenorrhœa.

Symptomatology.—The three clinical features which distinguish this tumor from other mammary tumors are the presence of a precursory tumor, rapid growth and attainment of unusual size. In Finsterer's eighteen cases, pain occurred in six instances; it was never present in the early stages but appeared only when rapid growth occurred with pressure and tension on the overlying skin. In our collective series the initial evidence in sixty-seven

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women was the discovery by the patient of a palpable lump in the breast. Two patients stated that the initial sign was a discharge from the nipple; this is quite infrequent and is not the usual accompaniment of cystosarcoma phyllodes. Only four patients stated that pain in the breast was the initial symptom, but nineteen complained of the presence of pain in later stages of the disease. Seven women complained chiefly of the great inconvenience caused by the weight of these heavy tumors. Only eight of the 109 patients had a constitutional impairment of health. The general health remains good in spite of the tumor. Cachexia, loss of weight and anæmia never occur unless ulceration, infection and hæmorrhage alter the local condition.

Physical Signs.—The usual giant intracanalicular myxoma of the breast is a bulky, freely movable, encapsulated, non-adherent tumor with bosselated nodulations, variable regions of fluctuations and resistance unaccompanied by retraction of the nipple or palpable axillary lymph-nodes. The lobulations and inequalities of the tumor are easily felt through the skin. The smallest tumors are smooth, even and regular in shape; occasionally they are disc-shaped. Fluctuation is frequently elicited in the superficial cysts. Unequal consistence of the tumor, some portions elastic and other parts firm and knobbed, is an important distinctive feature. A simple fibroadenoma may be found concomitantly in the opposite breast or in the same breast with the cystosarcoma phyllodes. (Birkett.) Semb reported an instance wherein multiple cystosarcomas developed about as many multiple fibroadenomas. The axillary lymph-nodes are not involved in the disease process, but they may become enlarged by inflammatory changes when ulceration and infection occur in the breast tumor.

Size.—In Finsterer's series of eighteen cases four of the tumors were as large as a man's head. In our collective series, eighteen of the tumors were said to be as large or larger than a human head. The actual weight of nineteen tumors was given, averaging 7.6 pounds each. These tumors are usually larger than a closed fist and they may weigh as much as 20 kilograms. (Ribbert.) When the tumor attains a great size, the major portion of the growth has taken place in one year.

Location.—Of fifty-nine tumors in which the location was mentioned thirty-eight were in the right and twenty-one were in the left breast. In twenty-six cases the location in the breast was mentioned; twelve were in the upper outer quadrant, four were in the lower outer quadrant, three in the lower inner quadrant, two in the upper inner quadrant and five occupied the central region of the breast.

Changes in the Skin of the Breast.—In Finsterer's eighteen patients the skin was adherent to four of the tumors and ulceration had occurred in three instances. In our collective series the status of the skin was mentioned in sixty-five case reports. Twenty-one had ulcerated lesions at the time of examination; four of these ulcerations were attributed to trauma. Five other tumors were adherent to the skin. In the remaining thirty-nine patients the skin was not ulcerated nor adherent to the tumor. In five patients rapid

fungation occurred once the skin had ruptured; in one instance an enormous cauliflower growth extruding within twelve hours' time. The capsule of the tumor and the superjacent skin may be ruptured by pressure necrosis induced by tension. The fungations which frequently result are not indicative of malignancy. The ulceration occurs at the lowest part of the tumor or at the point of greatest tension. Infection inevitably follows ulceration and at times gangrene ensues. Prior to rupture the skin is usually tense, smooth, shiny, dry, red, livid, cyanotic or violaceous. Enormous subcutaneous veins, often as thick as pencils, may radiate from the superficial vascular part of the tumor like a *caput medusæ*.

Nipple.—Retraction of the nipple is so very unusual that when it does occur the examiner suspects carcinoma rather than cystosarcoma. Poulsen emphatically declares that the nipple is never involved. In our collective series there is only one instance in which the nipple was retracted by the tumor; in another case the nipple was obliterated.

Precursory Tumor.—In fifty-seven of our collected case reports definite mention was made of a precursory tumor. Forty-seven of these patients gave a definite history of the presence of a precursory tumor in the breast. In ten instances a specific statement was made that no preëxisting tumor had been present according to the patient's knowledge.

Duration.—In Frangenheim's report the period of development averaged thirty-five to forty-eight months. In our collected series, there were seventy-five case reports in which this information was given. We found the average duration to be 6.7 years from the day of discovery to the date of examination. When these tumors exist for many years, they may remain inactive for a considerable portion of this time.

Rate of Growth.—Finsterer found cystosarcomas and true sarcomas to develop more slowly than carcinoma of the breast. The period between discovery and examination for these three tumors was given as follows: 25.5 months for cystosarcomas; 18.3 months for true sarcoma; 16.3 for carcinoma. True sarcoma of the breast was said to grow more rapidly than cystosarcoma. Helmuth in 1871 was the first to observe that cystosarcoma phyllodes grew with extreme rapidity with long intervals of arrested growth. The rate of growth was indicated in eighty-two of our collected case reports. In nine patients the tumor was of slow growth; on eight occasions the tumor grew at a moderate rate; in one instance the growth was slow with later a moderate increased rate; in twenty-six cases the tempo of growth was very rapid; in thirty-eight patients the tumors grew slowly or not at all for a long time and then exhibited sudden exacerbation of growth. In twenty-seven of these thirty-eight case reports wherein the actual time of the increased growth rate was mentioned, the average total duration of the tumor was 8.9 years, but the average time during which the tumor had shown the characteristic increased acceleration of growth was only 8 months.

Cystosarcoma Phyllodes—a Benign Tumor.—Cystosarcoma phyllodes is not a true sarcoma because it does not have a sarcomatous structure con-

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sistently, it does not metastasize commonly to viscera and it seldom recurs locally. Wulfig classifies this tumor as an entity somewhere between true sarcoma and simple fibroadenoma; he admits, however, that genuine and destructive sarcoma can develop in these tumors although it is commonly the sarcomatous type. Grohe made the statement that cystosarcoma phyllodes is as far removed from carcinoma as is condyloma of the penis. Schimmelbusch, Beneke and Haeckel emphasize the benign nature of cystosarcoma.

When the tumor perforates the skin it gives a false appearance of malignancy. The age of the patient, the rate of growth, the presence of pain and the occasional enlargement of the axillary lymph-nodes do not necessarily indicate a malignant neoplasm. Enlarged axillary lymph-nodes may be inflammatory.

It does seem, however, that sarcoma originates in cystosarcoma phyllodes more frequently than it does in the original fibroadenoma. Billroth reported two cystosarcomas which metastasized; however, there was insufficient microscopical description of these tumors to rule out genuine sarcomas. Theile's case report of cystosarcoma phyllodes mammae is unusual for although histologically verified sarcomatous metastases to bone occurred, sarcoma was not demonstrated in the primary breast tumor. Poulsen found that metastasis from true sarcoma of the breast occurred in 40 per cent. of patients, but observed recurrence or metastasis in only 25 per cent. of mammary cystosarcomas of all types. Prym removed a large breast tumor and after microscopical study in which no malignant areas were seen, diagnosed the tumor as cystosarcoma myxomatousum phyllodes. Two peculiar areas were seen, one of cholesteatoma and another of peculiar fat lobules in the centre of the original tumor, said to have been composed of immature lipoblasts. The tumor recurred locally and then metastasized to the lungs. The pulmonary metastases contained no epithelial elements. Prym described the metastases as myxosarcomatous but in the accompanying microphotographs the appearance suggests liposarcoma as well as myxosarcoma.

Of ninety-one cases in our collected series in which the outcome was mentioned, there were but six recurrences; one patient died from pulmonary metastases after a simple mastectomy; in three patients simple mastectomies were followed by recurrences which were excised; in one patient a recurrence followed a radical mastectomy; and in another, a local excision of the tumor was followed by a recurrence which was removed by simple mastectomy.

Differential Diagnosis.—Hemisection of the surgical specimen in the operating room reveals a gross appearance which is absolutely diagnostic and cannot be confused with any other tumor of the breast. The intracystic polypoid lobulations with narrow, tortuous clefts are not simulated by any other tumor except the intracanalicular fibroadenoma.

The clinical differentiation from carcinoma is not difficult. No cancer could grow so large without involving the skin. The encapsulation of the tumor, the freedom of the nipple, the lack of fixation and other evidences of

infiltration are important diagnostic features. The mobility of the skin over the tumor, the absence of the orange-peel type of skin and of regional distant metastases, as well as the maintenance of good general health, are diagnostic points in which cystosarcoma phyllodes differs from cancer. The three varieties of breast cancer which bear a faint resemblance to this tumor are the diffuse ductal carcinoma, the bulky adenocarcinoma and the intracystic papillary carcinoma. In the first-mentioned carcinoma the breast is diffusely invaded, the tumor margins are not easily definable, the nipple is invariably retracted and the skin of the entire breast is thickened and cedematous. The bulky adenocarcinoma which occurs more often in elderly subjects metastasizes late and often invades and ulcerates the skin; it may closely resemble cystosarcoma phyllodes. The intracystic papillary carcinoma originating in cysts or dilated ducts is often preceded or accompanied by a sanguineous discharge from the nipple. It is occasionally multiple and once its capsule is ruptured has the ability to infiltrate.

The carcinosarcoma of the breast is sometimes referred to as adenosarcoma. Many of these tumors are enormous; they may weigh ten to twenty pounds. They often ulcerate through the skin and the epithelial elements may metastasize to the axillary lymph-nodes. The round-cell sarcoma of the breast, including the lymphosarcoma, is softer than cystosarcoma, grows with greater rapidity and is many times more radiosensitive when subjected to the therapeutic test of irradiation.

The mixed tumors of the breast, according to Wilms, are of teratoid origin, developing from embryonal ectoderm and mesenchyme which are included in the mammary gland. These tumors may contain epidermis, cartilage and other structures indicating their origin from multiple germinal layers. Others say the mixed tumor is a metaplastic derivative of a benign tumor; in this sense there may be a histogenetic relation to cystosarcoma. Clinically they cannot be distinguished from encapsulated benign tumors of the breast such as large fibroadenomas, adenomas and cystosarcoma phyllodes. They are usually well delimited, encapsulated tumors, which remain small for a long time, then grow with great rapidity. They cause atrophy of the mammary gland proper without invasion. They do not adhere to the deep tissues nor do they metastasize by lymphatic vessels. They elevate and render the skin tense but never directly infiltrate the skin. They occur at all ages from twenty to seventy years.

An analogy exists between fibroadenomas, cystosarcoma phyllodes and chronic cystic mastitis because they have the same histological elementary or primary changes. They are differentiated by delimitation (cystosarcoma and fibroadenoma), by proliferation of epithelial tissue (fibroadenoma) and of connective tissue (cystosarcoma phyllodes). Chronic cystic mastitis is a more diffuse process and has few of the clinical features of a giant intracanalicular myxoma such as the rate of growth and bulky size. Tuberculous mastitis and mammary actinomycosis may be ruled out by the clinical history,

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by the physical findings upon examination and finally by an aspiration of the fluid content followed by microscopical diagnosis.

Prognosis.—The prognosis is usually good. It depends on: the type of cystosarcoma phyllodes, *i.e.*, whether cellular or myxomatous; the fixity of the tumor; the extent of the operation; the age and physical status of the patient; the presence of ulceration and infection; the duration and the size or local extent of the tumor.

Treatment.—The management par excellence is the prophylactic measure of removing all mammary fibroadenomas. If the tumors are small, local wide extirpation may be sufficient. If the tumor is incompletely removed it will recur. Billroth found that cystosarcoma phyllodes in young women



FIG. 3.—Case I. Clinical photograph. Note the bulk and delimitation of the tumor, the intact skin, the tortuous, dilated veins and the healthy appearance of the patient.

does not recur after removal but in older women (over thirty) he advises a more radical operation because of the danger of recurrence, or even transition to carcinoma. Such recurrences may be from residual portions of previous tumors or by the formation of new tumors. Hence it seems wiser in all cystosarcomas of considerable size to do a complete amputation of the breast, including the fascia over the pectoral muscles.

In ninety-one of our collected case reports the method of treatment is mentioned as follows: nine patients had radical mastectomies, forty-five had simple mastectomies, thirty-five had local excisions of the tumors, one had an intratumoral injection of phenol and another patient had a local mastectomy by the simple procedure of constricting the pendulous pedicled breast by a stout ligature.

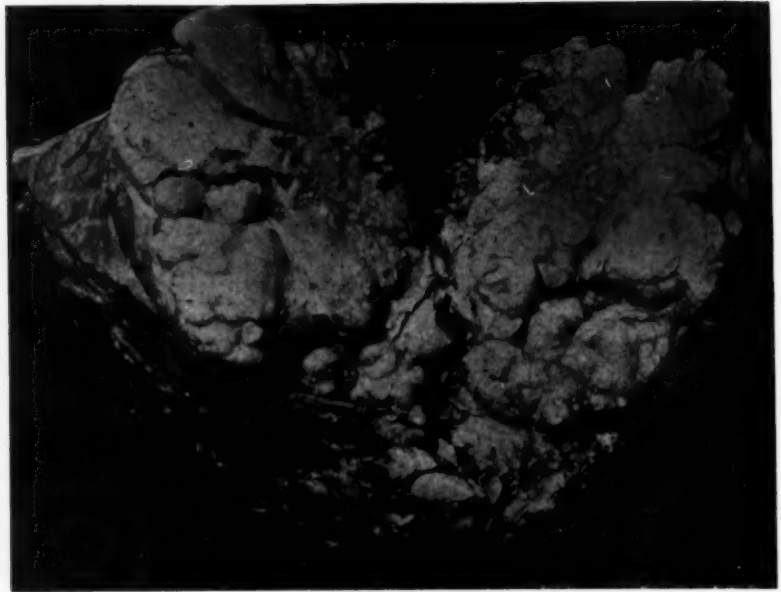


FIG. 4.—Case I. Gross specimen illustrating the large, intracystic myxomatous polyps separated by narrow, tortuous clefts.

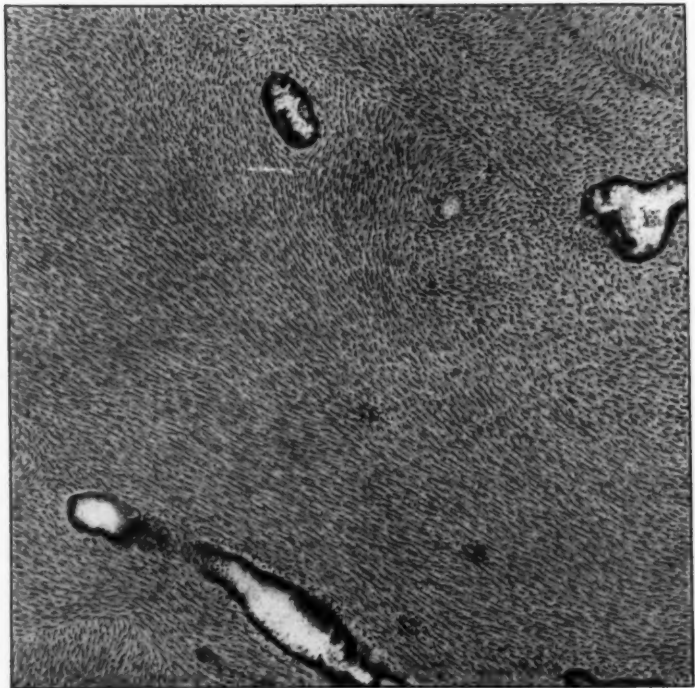


FIG. 5.—Case I. Densely cellular, pseudo-sarcomatous stroma surrounding glandular lacunæ.

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REPORTS OF CASES OBSERVED AT THE MEMORIAL HOSPITAL

CASE I.—D. K., a white, married woman, aged fifty-six years, applied to the Memorial Hospital December 3, 1927, complaining of a bulky tumor occupying the entire right breast.

Past History.—The patient was a diabetic. She had seven children, each of whom was nursed for at least two years without any lactational difficulties.

Present Illness.—Thirty-seven years previously (1890), following her first child-birth, the patient noticed a small lump beneath the right nipple. This nodule remained inactive until one year ago when it grew rapidly to occupy the entire breast. One month prior to examination there was an intermittent discharge of blood from the nipple.

Physical Examination.—The entire right breast was the seat of a bulky, lobulated, cystic tumor mass. The nipple was flattened but not retracted. There was no skin adherence and the tumor was freely movable with the breast. A radiograph of the chest was normal; heart and lungs were normal. The blood sugar was 146 milligrams per 100 cubic centimetres of blood. There was persistent albuminuria. The clinical diagnosis was papillary cystadenocarcinoma of the breast.

Treatment.—The patient refused operation until May 11, 1928, when a local mastectomy was performed, using a transverse elliptical incision. At this time the skin had ulcerated and the tumor was fungating. Convalescence was uneventful. Two years later there was no evidence of recurrence.

Gross Pathologic Anatomy.—The entire breast was occupied by a tumor mass, measuring 15 by 11 by 10 centimetres in diameter. The nipple was normal but displaced. Two and one-half centimetres from the areolar margin was a large ulceration, excavated to a depth of one centimetre. The floor of the ulcer was formed by soft tumor nodules. The tumor was invested by a thick fibrous capsule, the inner coat of which was perforated in certain regions. The tumor was composed of firm pearly-gray, gelatinous, intracanalicular polyps, with foci of caseation and calcification. The clefts between the polyps were filled with a thick, greenish fluid.

Pathologic Histology.—The stroma was pseudosarcomatous due to its cellularity. There were many interlacing bundles of spindle and fusiform cells. In some regions, the glandular structures resembled the sweat glands of the breast. The epithelium lining the ducts was in several layers. There was an abundant perivascular lymphocytic infiltration. Other degenerative changes were observed in regions containing small hemorrhages, hyaline metamorphoses and deposits of cholesterol crystals which were engulfed by syncytia of foreign-body giant cells.

CASE II.—B. S., a married Jewess, aged twenty-eight years, applied to the Memorial Hospital January 21, 1930, complaining of a rapidly growing lump in her right breast.

Past History.—Her father died with pneumonia at the age of seventy-nine years; her mother died of myocarditis at the age of sixty-four years. The patient had two children, aged four and two years. She nursed the first child thirteen months and the second child five months without any lactational difficulties.

Present Illness.—Three and one-half years previously (July, 1926), she felt a lump about 1 centimetre in diameter, medial to the right nipple. This lump remained inactive but persisted for three years until September, 1929, four months prior to admission, when the tumor began to grow with great rapidity and caused a peculiar dragging pain in the breast. She had not lost weight.

Physical Examination.—The patient was a well-developed, well-nourished white woman in good general condition. Her lungs were clear and resonant. Her heart was normal to physical examination. The liver was not palpable. The right breast was more prominent than the left and the central portion was occupied by a round tumor measuring 7 by 5 centimetres in diameter. The nipple was not retracted, the tumor was freely movable on the chest wall and the skin over it was not adherent. Its con-

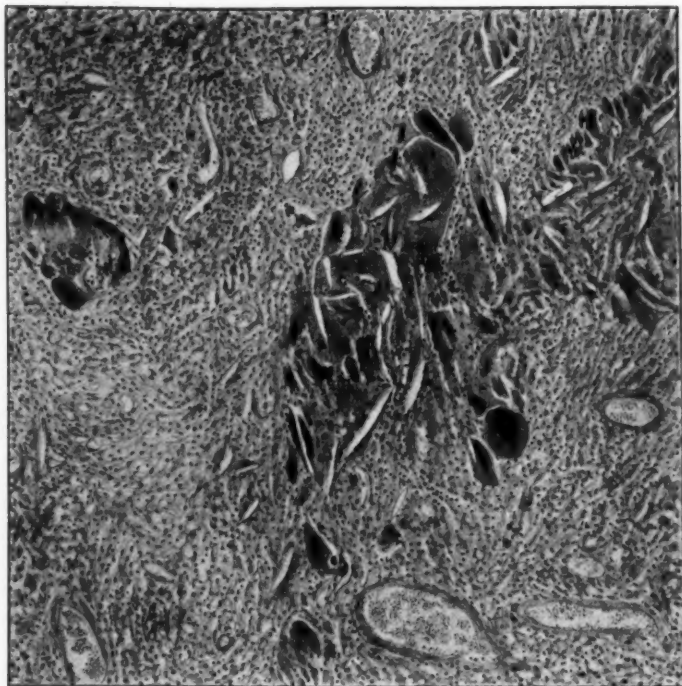


FIG. 6.—Case I. Xanthomatous region of tumor containing numerous crystals of cholesterol, engulfed by large, syncytial, foreign-body giant cells.



FIG. 7.—Case II. In this gross specimen, the intracranial polyps are firm, gray and striated, containing discrete, small, interstitial hemorrhages.

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sistence was firm and elastic. There were no palpable supraclavicular nor axillary lymph-nodes. The clinical diagnosis was fibroadenoma of the breast.

Treatment.—On January 31, 1930, a simple mastectomy was performed to include the pectoral fascia. Six months later there was no evidence of recurrence.

Gross Pathological Anatomy.—The tumor measured 9 by 7 by 5 centimetres in its diameter: Within its thick capsule were multiple soft, white, gelatinous polypoid intracystic projections. The polyps were closely approximated. Some portions of the tumor were myxomatous, others fatty, and still others hæmorrhagic. The breast proper was not invaded.



FIG. 8.—Case III. The polypoid masses have the characteristic fimbriated, phyllodic or cock's-comb appearance.

Pathologic Histology.—The stroma throughout the tumor was diffusely myxomatous. There was some hyaline degeneration of the connective-tissue type, surrounding the enlarged veins. Small hæmorrhages in the stroma were in the process of organization. There was perivascular infiltration of large mononuclear leucocytes which contained an abundance of brownish-yellow pigment granules. The glandular elements were more common than in most cystosarcomas; the tumor could be properly called an intracanalicular myxadenoma. The tall columnar cells lining the ducts rested on a layer of flat basal cells. Many of the ducts were dilated and contained colostrum corpuscles. In some regions the ductal epithelium was of the sweat-gland type, with intraductular papillary tufts of large columnar cells with eosinophilic cytoplasm.

CASE III.—S. K., a married Jewess, aged thirty-four years, applied to the Memorial

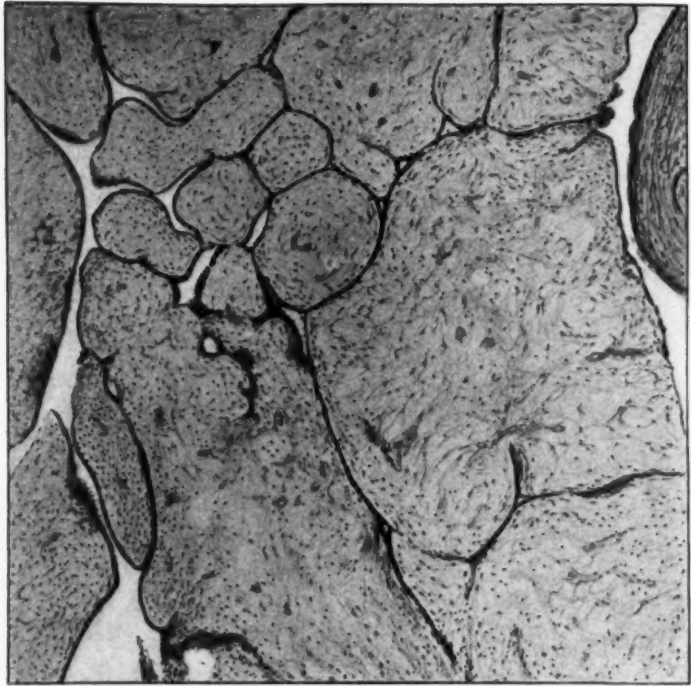


FIG. 9.—Case III. Cross-section of a typical intracanalicular myxoma.

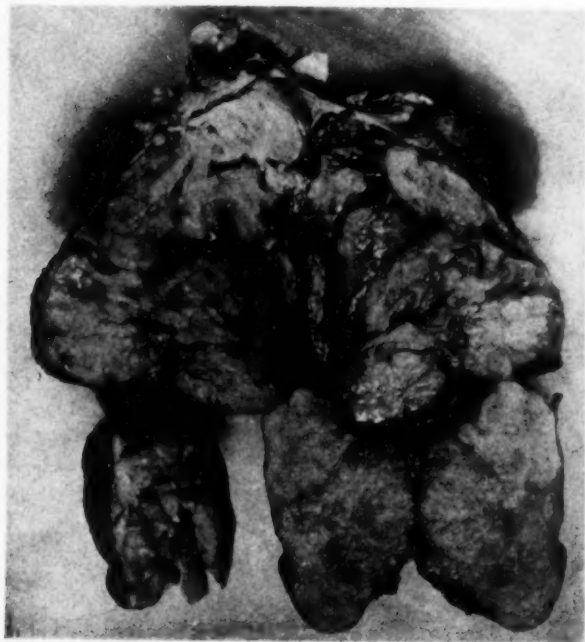


FIG. 10.—Case IV. This gross specimen exhibits the thin, delicate capsule, the multilocularity and the gelatinous character of the stroma of the cystosarcoma phyllodes.

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Hospital April 21, 1930, complaining of a rapidly growing lump involving the entire right breast.

Past History.—Her father died of heart disease at the age of fifty-two years and her mother was living and well. There was no history of cancer nor of benign breast tumors in the family. The patient has always been obese; her weight was 180 pounds. She was under treatment for hypertension. She had one child, aged fifteen years; she nursed this child only one month because of an abscess in the right breast; this abscess was incised at the lower edge of the breast.

Present Illness.—Nine years previously (1921), she first felt a small lump in the upper central portion of the right breast. This mass remained about the size of a hen's egg for nine years without discernible enlargement. Three months prior to examination (January, 1930), the right breast was struck upon the corner of a table. Following this injury there was ecchymosis over the upper part of the breast and the preëxisting lump began to enlarge very rapidly. There was some initial transient pain. The patient did not lose any weight and remained in good general health.

Physical Examination.—The entire right breast was involved by a bulky, nodular, semi-fluctuant, well delimited, ovoid, freely movable tumor measuring 16 by 12 by 10 centimetres in diameter. The nipple was flattened but not retracted. The skin was slightly adherent at one point toward the medial edge of the breast. There were no palpable lymphadenopathies. The subcutaneous veins were quite prominent and distended over the inner segment of the breast. A radiograph of the lungs was negative for metastasis of carcinoma.

Treatment.—A cycle of four high voltage X-ray treatments was given over the right breast to include the axillary and supraclavicular spaces. There was only slight regression in the size of the tumor following these treatments. May 9, 1930, a right radical mastectomy was done using a transverse Stewart incision. The axilla was dissected completely and the pectoral muscles were removed with the breast. Three months later there was no evidence of recurrence.

Gross Pathologic Anatomy.—The tumor measured 16 by 10 by 9 centimetres in its diameters. Its capsule was distended and in contact with the skin of the breast. There was some spontaneous necrosis within the tumor, and the clefts contained a brownish fluid. The intracystic cauliflower projections showed regions of myxomatous, xanthomatous and fatty degeneration.

Pathologic Histology.—The histologic arrangement of the tumor was that of a typical intracanalicular myxoma. The myxomatous changes were limited to the periductal tissues. In some regions the stroma was densely cellular with fusiform cells of uniform type. There was also some calcareous degeneration and hyaline changes in the stroma.

CASE IV.—T. B., a single Italian woman aged forty years, had noticed a gradual progressive enlargement of both breasts during the last ten years. In the last few months the tumors in both breasts grew with great rapidity. She suffered an occasional dull pain in both breasts. Her menstrual history was normal; she had never been pregnant.

Her younger sister had a mammary tumor excised five years previously at another institution. This tumor was said to be a cystosarcoma phyllodes.

January 20, 1930, the tumors in both breasts were excised by Dr. M. Caturani, at the Parkway Hospital, New York. Convalescence was uneventful. There has been no recurrence. We are indebted to Doctor Caturani for permission to study this tumor.

Gross Pathologic Anatomy.—In the left breast the tumor measured 13 by 11 centimetres in diameters, and in the right breast the other tumor was the size of a small orange. Both tumors were encapsulated, lobulated, intracanalicular polypoid myxomas.

Pathologic Histology.—The gross architecture of the tumor resembled the well-known intracanalicular fibroadenoma. The myxomatous changes were not confined to the periductal tissue which forms the polypoid masses but also were found in the

deeper stroma. Many of the polyps had undergone hyaline metamorphosis, but retained their epithelial investments. Dilated, delicate, embryonal blood-vessels occupied the centre of these polyps, many of which were œdematous. The clefts were lined by two layers of epithelial cells, the flat basal-cell layer and a superficial epithelium as hyperplastic as to simulate intraductular carcinoma.

SUMMARY

After a study of 109 cases of giant intracanalicular myxoma of the breast (cystosarcoma phyllodes), we may summarize the salient characteristics of this tumor as follows:

1. Great size, averaging 7.6 pounds.
2. Lobular shape, with variable regions of fluctuation and resistance.
3. Encapsulation.
4. Mobility and usual non-adherence to skin and fascia.
5. No retraction of nipple and no involvement of axillary lymph-nodes.
6. Possible occurrence in males (3 per cent.).
7. Development from preëxistent fibroadenomas, probably intracanalicular fibroadenomas.
8. Important rôle of lactation and nursing difficulties in this metamorphosis.
9. Long duration, averaging 6.7 years.
10. Long initial period of quiescence or slow growth, followed by sudden rapid acceleration.
11. Intracystic polypoid excrescences moulded by apposition with each other.
12. Narrow, sinuous, distorted clefts between the polyps.
13. Myxomatous stroma with cellular pseudosarcomatous regions.
14. Benignity; good prognosis with freedom from recurrence.
15. Successful treatment by wide local excision or simple mastectomy.

THE RESULTS OF TREATMENT OF CANCER OF THE BREAST

BASED ON A STUDY OF 489 CASES—1914-1925

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FROM THE STATE INSTITUTE FOR THE STUDY OF MALIGNANT DISEASE

THERE is probably no other disease which the surgeon and radiologist are called upon to treat that is more discouraging, at times, than cancer of the breast. Professor Ewing¹ has summed up the difficulties in the treatment of this disease and I believe that a quotation of his statement is very timely: "From clinical and pathological studies I have drawn the impression that, in dealing with mammary cancer, surgery meets with more peculiar difficulties and uncertainties than with almost any other form of the disease. The anatomical types of the disease are so numerous, the variations in clinical course so wide, the paths of dissemination so free and diverse, the difficulties of determining the actual condition so complex, and the sacrifice of tissue so great, as to render impossible in a majority of cases a reasonably accurate adjustment of means to ends."

My experience leads me to agree with Doctor Ewing and I feel that those who have to deal with this group of cases must not be too optimistic, for pessimism is sure to follow when the vagaries and freakishness of the metastases manifest themselves. Every surgeon and radiologist has learned to regard cancer of the breast as being one of the most tricky and difficult diseases to prognosticate. Such eminent American authorities as Doctors Halsted,² Willy Meyer,³ Greenough,⁴ Bloodgood,⁵ and Lee,⁶ as well as such eminent foreign authorities as Mr. Handley,⁷ Professor Wintz,⁸ and Forsell and his associates at Radiumhemmet,⁹ have at various times contributed greatly to the advancement of our knowledge of this disease. Handley's work on cancer of the breast, in which he so clearly demonstrates the channels of dissemination through the lymphatics, is a monumental contribution in the advancement of our knowledge. Doctor Ewing's summary, as quoted above, bears out the logic of Handley's investigations. Mr. Handley's clear vision of the pathology from the surgical point of view brings to our attention very forcibly how inadequate is the so-called radical operation as advocated by Willy Meyer, Rodman or Halsted. If it were only that cancer of the breast disseminated itself along lines which the radical operation can eliminate, one would be more satisfied with the possibilities of such an operation. Too often one is chagrined, after a period of one to ten years, to find dissemination of the original tumor appearing along the second, third and fourth intercostal spaces, near the sternum, or to find mediastinal and pleural involvement, or widespread or isolated bone metastases. Mr. Handley's

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point is well taken in the technic of applying radium after radical operation in trying to eradicate the possible metastases to the anterior mediastinum. It has been my misfortune to see recurrences in this locality in numerous instances, appearing after years, some as late as seven, eight and nine years; as well as to see metastases in the supraclavicular lymph nodes, the mediastinum or the bones, on a few occasions thirteen, fifteen and twenty years after the original operation.

After my experience with cancer in general I am more and more inclined to believe that the word "cure," as applied to malignant disease, should be eliminated from the literature and the words "clinically well" be substituted.¹⁰ The value of any therapy should be judged purely on the basis of comfort to the individual and the prolongation of life, even though the disease has not been eliminated from a pathological point of view. Whether this result

TABLE I

Results of Operation in Carcinoma of the Breast without Irradiation and with Irradiation
(This is part of a table which appeared in a recent article by Pfahler and Parry¹¹)

Author	Without gland involvement		With gland involvement	
	Operation without irradiation Per cent.	Operation with irradiation Per cent.	Operation without irradiation Per cent.	Operation with irradiation Per cent.
König.....	100		39	
Bloodgood.....	70		20	
Lee.....			15	
Finisterer.....			4.3	
Doderlein.....	46	48	5	20
Doderlein (completed).....		80		36
Wintz.....		77		
Schmitz.....		64		42
Perthes.....			25	
Anschutz.....	100	100	31	42
Harrington.....	70.5	66.2	22.8	22.3
Pfahler and Parry.....		89		47
Schreiner.....		65		23

can be obtained by a given procedure or by a combination of procedures is of paramount importance. I believe that conservatism in surgery, together with radiation and other medicaments, may be the means to this end.

It should be our earnest endeavor to establish the limits of surgery as a possibility of eradicating cancer of the breast. The greatest discrepancies are seen in the statistical reports of competent observers,¹¹ Table I. Doctors Steinthal, Lee,¹² and Schmitz,¹³ together with others, have tried to establish clinical groupings so that the results of cases reported in the literature can be better estimated. If all should decide on a grouping and classify their cases accordingly the statistics of five years hence would be more accurate and of the greatest value.

With this thought in mind I have separated these cases into primary carcinoma of the breast and post-operative recurrent carcinoma of the breast.

RESULTS OF BREAST CANCER TREATMENT

The *primary cases* are divided into three groups. Group I consists of those cases in which the growth is confined to the breast and having no metastases, as evidenced by clinical and radiographic examinations, as well as, in the operative cases, by histological examination. In Group II are all carcinomas of the breast with definite metastases in the axilla, or ulceration of the breast which is fixed to the pectoral muscle, and showing without doubt involvement of the skin lymphatics. In Group III are the tumors of the breast, with or without axillary involvement, but with definite widespread metastases, as in the supraclavicular region, mediastinal or disseminated metastases. The *recurring carcinomas* of the breast are divided, as accurately as possible, into two groups. In Group I are those with local recurrence only; in Group II those with or without local recurrence but with disseminated metastases.

There were 480 cases of carcinoma of the breast admitted to the State Institute for the Study of Malignant Disease from 1914 to 1925. Of these 480 cases 283 were *primary* and were divided as follows: In Group I were seventy-one cases, fifty-two of which were treated by radical operation and

TABLE II
Showing Age Incidence at the Time of Admission

	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99	Total
Primary Group I....	—	5	23	23	11	7	2	—	71
Primary Group II....	3	10	24	38	36	16	5	—	132
Primary Group III....	—	6	13	25	20	12	3	1	80
Recurring Group I....	—	3	9	13	5	1	—	—	31
Recurring Group II....	2	17	57	55	29	6	—	—	166
Total.....	5	41	126	154	101	42	10	1	480

radiation, and nineteen treated by radiation alone. In Group II there were 132 cases, fifty-three of which were treated by radical operation and radiation, and seventy-nine by radiation alone. Most of these seventy-nine cases were, for one or more reasons, considered *not* suitable for operation. In Group III there were eighty cases. These were definitely inoperable and were treated by radiation alone. Of the 480 cases 197 were *recurrences*. These were divided as follows: In Group I, thirty-one cases with local recurrence only, treated by radiation alone, and 166 cases in Group II, local recurrence and disseminated metastases, which were treated by radiation alone.

The age incidence is depicted in Table II. The youngest patient was twenty-four, the oldest ninety years of age. Fifty-eight per cent. were between forty and sixty years old. These 480 patients were females, 388 of them being married, and ninety-two single. The disease was primary in the right breast in 214 cases, in the left breast in 231 cases; in thirty-five instances both breasts were involved, twenty-one of these being post-operative, recurring cases of Group II. A history of cancer in the family was reported by 110 of these women. The blood Wassermann reaction was positive in thirty-eight of these patients. Eighty-nine of these women gave a history of injury,

either in the form of a blow, a kick, fall or bruise, which they thought might have contributed to, or been the cause of, their trouble. Sixty-four per cent. of these patients gave a history of less than one year's duration at the time of admission, 77 per cent. of less than two years' duration. One hundred forty-three of these women had never been pregnant, the other 337 gave a history of from one to nine pregnancies.

Treatment.—Prior to 1920 these patients were treated with low voltage X-rays in divided doses, $2\frac{1}{2}$ millimetres aluminum filter, 100,000 volts, 5 milliamperes, time factors varying from five to fifteen minutes at 20 to 30 centimetres' distance. Treatment was repeated sometimes at one-week intervals or two-week intervals over a period of one to three years, with intervals of rest depending on the condition of the skin.

From 1920 to 1925 the patients were treated by means of high voltage X-rays with varying technic as to distance and number of fields applied. During the years 1920, 1921 and 1922, cross-firing and massive doses were tried and resulted in much depression, X-ray sickness, and on the whole did not seem to justify the procedure that was then carried out. From 1923 to 1925 divided high-voltage X-rays were used which seemed more beneficial to the patients. The method was to divide a known quantity of X-rays over a period of a week to twelve days, allowing for the time elapsed between treatments; the desire being to administer from 120 to 150 per cent. on the skin. The factors of high-voltage X-rays were: 200,000 volts, 8 to 30 milliamperes, 0.5 millimetre copper, 1 millimetre aluminum filter, size of field 10 by 15 up to 20 by 20 centimetres, distance 40 to 50 centimetres, time factor depending on milliamperage and distance.

In some cases the implantation of radium emanation in glass seeds was resorted to. In a few cases radium packs were substituted for high-voltage X-rays, the factors being 6 centimetres' distance, 2 millimetres of brass, 1 millimetre of aluminum, 1 centimetre of rubber, for 6,000 to 8,000 millicurie hours per field.

In the cases which were operated, the radical operation according to the method of Willy Meyer was carried out.

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480 cases treated. 283 *primary cases*. 52 cases in Group I were treated by *radical operation* and *radiation*. 4 of these died of intercurrent disease, having been clinically well one year, one year, three months, one year, six months, and for two years, seven months, respectively. 2 were lost trace of. 1 had been clinically well four years, the other one had a recurrence and was lost trace of in less than a year. 46 cases were available for study. 35 of these lived for from five to sixteen years from the time of treatment. 30 of the 46 cases, or 65 per cent., have been clinically well for five years or more. 1 has lived eight years. She was clinically well four years, ten months, when there was a recurrence in the scar which has healed twice since with radiation (for one year each time). Now the scar is thickened and adherent to the chest wall but she is feeling well. 1 died eight years after treatment. She had been clinically well two years, eight months following treatment when there was a recurrence in the axillary scar which responded to radiation and she was

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again well for two years, four months when she developed spinal and mediastinal metastases which caused her death, there being no evidence of recurrence externally. 1 died five years after treatment. She developed mediastinal metastases two years, three months after treatment, the operative site remaining well at the time of death. 1 died in five years. She had been clinically well four years when metastases developed in the supraclavicular region, thyroid and sternomastoid muscle. 1 is alive five years after treatment. Two years after treatment she developed mediastinal nodes, followed by glandular involvement of both hila and four years after treatment there was metastasis in the supraclavicular region. The operative site remains well.

11 patients died in less than five years. In 8 the operative site remained well but metastases developed and they died as follows: 1 in nine months from mediastinal metastases; 4 in from one to two years, 1 from liver metastases, 1 from metastases to the brain and mediastinum; 1 from metastases to the supraclavicular region and liver, 1 from metastases in pancreas and liver. 1 in from two to three years from liver metastases. 2 in from three to four years; 1 from carcinoma of the other breast and metastases in the supraclavicular region and mediastinum, 1 from metastases in the liver. 3 patients had local recurrence and metastases and died: 2 in from one to two years from recurrence and general metastases; 1 in four years nine months. She had been clinically well one year, two months, when there was a recurrence over the fourth rib which gradually extended over the chest and into the mediastinum.

19 cases in Group I were treated by *radiation only*. 3 died of intercurrent disease in one year, two years, and in two years, seven months, respectively, 2 being clinically well, the other much improved. 2 were lost trace of in less than a year. 14 cases available for study. 6 of these lived for five years or more. 4 of the 14 cases, or 28 per cent., have been clinically well five years or more. 1 is living eight years, eight months from the time of admission. She has had supraclavicular and axillary nodes for the past two years. 1 died six years from the time of admission. She had been clinically well two years, five months when there was a recurrence locally, followed by definite mediastinal involvement four years after admission. 8 patients died in less than five years: 1 in less than one year, unimproved; 2 in from one to two years, 1 unimproved, the other from carcinoma of the stomach, the breast lesion having healed; 2 in from two to three years, unimproved; 1 in from three to four years, having been clinically well one year, nine months when there was local recurrence; 2 in from four to five years, 1 had been clinically well one year when there was local recurrence, 1 died from mediastinal and spinal metastases, the breast having never entirely healed.

Nine of the 19 cases, or 47 per cent., showed marked improvement, which, however, was not lasting.

53 cases in Group II were treated by *radical operation and radiation*. 4 died of intercurrent disease, 3 having been clinically well six months, ten months and two and a half years, respectively; 1 in one and a half years, after recurrence. 6 were lost trace of in less than a year. 3 had had recurrence. 3 were clinically well when last seen. 43 cases available for study. 15 lived for from five to ten years. 10 of the 43, or 23 per cent., have been clinically well five years or more. 1 was clinically well for one year when there was a local recurrence and she died in five years. 1 was clinically well for four years when there was a local recurrence and distant metastases developed and they died as follows: 2 in less than one year, 1 from five years. 1 was clinically well two years when there were definite skin metastases which became progressively worse and she died from mediastinal metastases five years from the time of admission. 1 was clinically well four years, two months when there was local recurrence. She died six years, nine months from the time of admission. 1 is living eight years after admission. She developed a recurrent

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- node in the axilla three months after treatment, and a recurrence in the scar in the chest four years, three months after treatment.
- 28 patients died in less than five years. In 5 the operative site remained well but metastases developed and they died as follows: 2 in less than one year, 1 from abdominal metastases, 1 from liver and spinal metastases; 2 in from two to three years, 1 from mediastinal metastases, 1 from abdominal metastases; 1 in from four to five years, having been clinically well three years, six months when she developed spinal metastases.
- 23 patients had local recurrence and metastases and died as follows: 6 in less than one year, 8 in from one to two years, 3 in from two to three years, 4 in from three to four years, 2 in from four to five years. One of these had been clinically well one year, seven months when there was a recurrent node in the axilla, definite recurrence in the scar not appearing until four years, five months after treatment.
- 79 cases in Group II were treated by *radiation only*: 7 were unimproved and lost trace of in from a few months to three years. 3 died from intercurrent disease, all improved, 2 in three months, 1 in one year, eight months. 69 cases were available for study. 10 have lived for from five to nine years. 1 of the 69 cases, or 1.4 per cent., has been clinically well five years. 1 was clinically well three years when skin nodules appeared and the condition has remained the same. 1 died in five years, five months from the disease and metastases. 1 died in five years from intercurrent disease. There had been no clinical evidence of the disease for a period of four months prior to death. 1 died in six years from the disease. 1 died in six years, four months from mediastinal metastases; local improvement. 1 was clinically well one year, eight months when there was local recurrence and she died six years, seven months from the time of admission. 1 was clinically well two years when there was local recurrence and she died in seven years from the time of admission. 1 was clinically well one year when there was mediastinal involvement, followed in two years by local recurrence. She feels well eight years after admission; there is a hard sclerosed tumor in the breast. 1 was clinically well three years, eight months when there was local recurrence and metastases over the whole chest. She died eight years, two months from the time of admission.
- 59 patients died in less than five years; 17 in less than one year. In one the breast was healed and she died from carcinoma of the uterus. 14 died in from one to two years. 12 were unimproved. 2 had been clinically well eight months and one year, eight months, respectively, when there was local recurrence. 9 died in from two to three years. 7 were unimproved. 1 died from metastases in the liver and uterus, having been clinically well two years. 1 died from distant metastases, the node in the axilla had persisted but the breast healed. 13 died in from three to four years. 12 had palliation only. 1 was clinically well three years when there was local recurrence as well as metastases. 6 died in from four to five years; all had had good palliation.
- 80 cases in Group III were treated by *radiation only*: 7 were lost trace of. 4 in less than a year, 2 in from one to two years, 1 in from four to five years. 73 cases available for study. 2 patients are living over five years: 1 for six years from the time of admission, she has had marked regression in the primary tumor and in the metastases in the supraclavicular and axillary regions, mediastinal metastases still present; 1 for seven years, she had supraclavicular nodes on admission and has been clinically well for the past three years. 71 patients died in less than five years as follows: 33 in less than one year; 20 in from one to two years; 6 in from two to three years; 6 in from three to four years, one of these had been clinically well three years when there was local recurrence and metastases in the liver; 6 died in from four to five years, one of these had lung involvement at the time of admission, the breast lesion had been healed for two years prior to death.

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- 197 *recurring cases.* 31 cases in Group I were treated by *radiation only*: 2 died of intercurrent disease, having been clinically well one and a half years and two years, respectively. 3 were lost trace of in less than one year. 26 cases available for study. All died in less than five years from the recurrence and metastases as follows: 11 in less than one year, 9 in from one to two years (2 of these had seemed clinically well for a few months), 4 in from two to three years, 2 in from four to five years. One of these had been clinically well for two years when there was local recurrence as well as metastases.
- 166 cases in Group II were treated by *radiation only*: 29 were lost trace of, 28 in less than one year, only one having shown improvement. 1 in two years. 137 cases were available for study: 6 of these lived five to seven years: 1 has been alive for five years from the time of admission. She had mediastinal metastases and nodes in the scar at the time of admission; these healed with X-ray treatment for nine months. 1 has been alive for five years. She had supraclavicular nodes at the time of admission which were held in check by radiation. She developed mediastinal metastases two years after admission. 3 died in from six to seven years, 1 showed marked regression of the local recurrence, palliation lasting up to seven years. 1 had marked palliation for over three years, 1 died from mediastinal metastases, there having been no local recurrence for three years prior to death; 1 patient is living seven years, three months, from the time of admission. There has been marked regression of the metastases in the supraclavicular region, although we are suspicious that there is now mediastinal involvement. 82 died in less than one year. 37 in from one to two years. 6 in from two to three years (one of these had marked palliation). 6 in from three to four years (one showed marked regression of the metastases, another was well externally for three years when she died from the mediastinal involvement which she had at the time of admission).

SUMMARY

The *absolute statistics* of the 283 primary cases show that forty-five, or 16 per cent., have been clinically well for five years or more; that thirty, or 58 per cent., of the fifty-two primary Group I cases, treated by operation and radiation, have been clinically well five years or more; that four, or 21 per cent., of the nineteen primary Group I cases, treated by radiation only, have been clinically well five years or more; that ten, or 19 per cent., of the fifty-three primary Group II cases, treated by operation and radiation, have been clinically well five years or more; that one, or 1.2 per cent., of the seventy-nine primary Group II cases, treated by radiation only, has been clinically well five years or more. No case in primary Group III, treated by radiation only, has been clinically well five years. No case in the recurrent Group I, or recurrent Group II, treated by radiation only, has been clinically well for five years.

Statistics based on patients available for study:

Primary Group I.—Of forty-six cases treated by operation and radiation, thirty, or 65 per cent., have remained clinically well for five years or more. Of fourteen cases treated by radiation only four, or 28 per cent., have remained clinically well for five years or more.

Primary Group II.—Of forty-three cases treated by operation and radiation, ten, or 23 per cent., have remained clinically well for five years or more.

Of sixty-nine cases treated by radiation only, one, or 1.4 per cent., has remained clinically well five years or more.

Primary Group III.—Palliations are shown in this group of seventy-three cases in the longevity of the patients. From the time of admission: 2½ per cent. lived five years or more; 8 per cent. died in from four to five years; 8 per cent. died in from three to four years; 8 per cent. died in from two to three years; 27 per cent. died in from one to two years; 45 per cent. died in less than one year.

Recurrent Group I.—Of twenty-six patients, treated by radiation only, from the time of admission: 7.6 per cent. died in from four to five years; 15.3 per cent. died in from two to three years; 34.6 per cent. died in from one to two years; 42.3 per cent. died in less than one year.

Recurrent Group II.—Of 137 patients, treated by radiation only, from the time of admission: 4.3 per cent. lived over five years; 4.3 per cent. died in from three to four years; 4.3 per cent. died in from two to three years; 27.0 per cent. died in from one to two years; 59.8 per cent. died in less than one year.

CONCLUSIONS

1. In primary operable Group I cases, treated by radical operation and radiation, 65 per cent. of those available for study were clinically well five years or more; of those treated by radiation alone, 28 per cent. remained clinically well five years or more.

2. In primary Group II cases, treated by radical operation and radiation, 23 per cent. have remained clinically well five years or more; of those treated by radiation alone (which were inoperable) 1.2 per cent. remained clinically well five years or more.

3. The primary Group III cases, treated by radiation alone, have yielded palliations only.

4. The recurring cases, Group I and Group II, treated by radiation alone, have yielded palliations only.

5. I am convinced that irradiation is of distinct value in the retardation of the growth and the amelioration of suffering and in the prolongation of life.

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METASTASES TO THE SKELETON, BRAIN AND SPINAL CORD FROM CANCER OF THE BREAST AND THE EFFECT OF RADIOTHERAPY

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THE clinical course and response to therapy of metastases from cancer of the breast may best be studied in patients whose histories are known from the time of discovery of the tumor to the time of death. Patients alive when they are investigated or those dying accidentally or from intercurrent diseases, illustrate only single chapters in the life history of the cancer and do not give a true picture of the disease as a whole.

The greater number of patients with cancer of the breast admitted to the Radiotherapeutic and Surgical Services of the Montefiore Hospital of New York during the past ten years, reached the hospital in the terminal stage of the disease. They died shortly after, either in the hospital or at home while under direct or indirect supervision of the medical staff of these services. The clinical course of the earlier phases of the disease had to be reconstructed in most cases from the history as given by the patient or from records of other hospitals. Through the coöperation of the departments of pathology of Montefiore Hospital and several other hospitals, histological studies on the original tumor and its metastases were made possible in nearly four-fifths of the cases.*

Material.—One hundred and sixty-eight cases of carcinoma of the breast with metastases to various parts of the body were studied from the time of the discovery of the tumor to the time of death. Nearly half (eighty-one cases) had skeletal metastases, proven röntgenographically or at autopsy. More than half of these had involvement of the lumbosacral spine and about one third of the skull. Of the latter, more than half gave neurologic signs

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of brain involvement and of the former, thirteen cases were thought to have spinal-cord metastases. No cases of spinal-cord involvement were observed in the absence of evidence of the disease in the lumbosacral spine. It is doubtful whether true metastases to the spinal cord occurred, in as much as autopsy of four of the thirteen showed, in three only compression of and in one an extension into the cord. A similar problem arose with regard to brain involvement: in nine autopsies, extension from the calvarium to the dura was found in one, extension from the calvarium through the dura to the brain in three, and multiple metastases apparently spread by the blood-stream in five. It can thus be seen that clinical differentiation of compression, extension and true metastases from carcinoma of the breast in the central nervous system is difficult if not impossible. Of the eighty-five cases of metastases to the skeleton and central nervous system, sixty-seven were verified histologically; thirty-two of these were examined post-mortem. Sixty cases of the eighty-five could be grouped according to histological evidence of malignancy, into Grade I, or least malignant, Grade II, or moderately malignant, and Grade III or most malignant. Of the eighty-five cases nearly 66 per cent. (fifty-six cases) had radical mastectomies; 15 per cent. (thirteen cases) were not operated upon; 8 per cent. (seven cases) had simple mastectomies, and 6 per cent. (five cases) had only biopsies. Many cases were so far advanced when admitted to the Montefiore Hospital that radiotherapy was withheld, or one X-ray treatment given for psychological reasons. These latter cases have not been used in evaluating the efficiency of radiotherapy.

Definitions.—The term of life of the patient, from the time of the discovery of the primary tumor to death, was divided into two periods. The last third was designated as terminal in contrast to the earlier two-thirds or pre-terminal. An exception was made in the case of patients who lived over three years. In these, the last year of life was looked upon as the terminal stage. It was found that at least 55 per cent. of the cases of skeletal metastases occurred during the pre-terminal period of the disease, and that survival in this group after the appearance of clinical evidence of skeletal metastases varied from a few months in fulminating cases to four and two-thirds years in the slowly advancing carcinomas.

Our criterion for clinical evidence of skeletal metastases was pain or tenderness localized in a part of a bone which later showed the typical röntgenographic picture of metastasis, or in which cancer was found at autopsy. All of the cases quoted in this paper as skeletal metastases have been thus verified. The clinical diagnosis of brain and cord involvement was based on symptoms of increased intracranial pressure or neurologic signs of localized cerebral, cerebellar, brain stem or cord involvement. The difficulty of differentiating between compression, extension and true metastases in this connection has already been mentioned. Clinical diagnosis of pulmonary and pleural metastases was made on subjective symptoms or physical signs of a process in the lungs which could not be explained on other grounds, and in which later, röntgenographic or post-mortem evidence of cancer was found.

Under skin metastases, were included typical cutaneous and subcutaneous nodules in or near the operative scar, or related to a carcinomatous ulcer. Direct extension from a broken-down carcinomatous ulcer of the skin was excluded, as it was felt that this was not a true metastasis. In spite of probable errors and the incompleteness of individual case histories, it is believed that the sum total of information gathered allows certain general conclusions which hold true for the average case of carcinoma of the breast with metastases to the skeletal and central nervous systems.

Sex, Age, Location of Primary Tumor.—Of the eighty-one cases with skeletal metastases, eighty were in women and one was in a man.

The age of the patients when the tumor was first noted, varied from twenty-two to seventy-five years. As seen from Table I the greatest number of cases occurred between the ages of forty and fifty years. A definite relationship between age and duration of life following the discovery of the tumor could not be established. Several of our youngest patients were among those who lived for a long period while some of the oldest patients died soon after the discovery of the tumor.

TABLE I
Age When Tumor Was Noted—81 Cases

Age Groups	Per cent. of cases
Under 30	5
30-40	30
40-50	37
50-60	19
60-70	8
Above 70	1

The primary tumor arose in the right breast in forty-three cases and in the left breast in thirty-eight cases. Data giving more exact localization of the tumor in the breast were too incomplete to be of much value. Information regarding clinical or microscopical involvement of axillary lymph-nodes was frequently so unsatisfactory that it was decided to leave this factor also out of consideration.

Anatomical Distribution of Skeletal Metastases.—Among the eighty-one patients there were only 16 per cent. (thirteen cases) that apparently had metastases to the skeleton alone. In the rest, *i.e.* 84 per cent. (sixty-eight cases) skeletal invasion was associated with metastases to one or several of the other body systems. The distribution of these metastases in eighty-one cases was as follows: lungs 52 per cent. (forty-two cases), skin 36 per cent. (twenty-nine cases), brain 21 per cent. (seventeen cases), spinal cord 16 per cent. (thirteen cases).

Most of the skeletal metastases were multiple. Of the eighty-one cases only fourteen showed involvement of a single bone, and even in these it may be questioned whether some other metastasis was not overlooked.

The regional distribution of the metastases was investigated, first as to

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general distribution, and secondly as to the site of the first localization. The latter study probably gives a truer picture of the predilection of the metastatic process for certain bones especially if the pre-terminal cases are considered separately.

TABLE II
*Anatomical Distribution in 81 Cases of Skeletal Metastases**

General localization	Per cent.	No. of cases	Specific localization	Per cent.	No. of cases	Homolateral† Heterolateral Bilateral
Pelvis.....	62	51	Ischium..	37	19	
			Ilium....	58	30	
			Pubis....	56	29	
Spine.....	59	48	Cervical..	13	8	
			Dorsal...	40	24	
			Lumbar...	57	34	
			Sacral....	38	23	
Femur.....	54	44				Bilateral..... 31 Heterolateral.. 8 Homolateral.. 5
Ribs.....	39	32				Bilateral..... 20 Heterolateral.. 5 Homolateral.. 7
Skull.....	35	29				
Humerus.....	27	22				Bilateral..... 11 Heterolateral.. 5 Homolateral.. 6
Scapula.....	16	13				Bilateral..... 8 Heterolateral.. 4 Homolateral.. 1
Clavicle.....	14	12				Homolateral.. 1 Bilateral..... 5 Heterolateral.. 6
Tibia.....	3	3				Homolateral.. 2 Heterolateral.. 1
Sternum.....	1	1				
Radius.....	1	1				
Ulna.....	1	1				
Hands.....	1	1				
Fibula.....	1	1				
Bones of Feet.....	1	1				

NOTE.—* Most of the cases had multiple metastases, so that the same case may appear under several headings. A clearer picture of the relative frequency may be obtained from Table III.

† "Homolateral" designates occurrence on the same side as the primary growth in the breast; e.g. right breast and right femur; "Heterolateral" on the opposite side.

Of the forty-five cases of skeletal metastases occurring in the pre-terminal stage the skeleton was the primary localization in 82 per cent. (thirty-nine cases). In only six cases did röntgenographic or clinical evidence of other metastases precede skeletal invasion; in three these were pulmonary and in three cutaneous metastases. The metastases however did not remain localized

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TABLE III

The First Site of Involvement as Suggested by Pain and Later Confirmed Röntgenographically.
75 Cases

	Per cent.	No. Cases
Sacro-lumbar spine.....	37	28
Femur.....	16	12
Pelvis.....	14	11
Skull.....	13	10
Dorsal spine.....	5	4
Ribs.....	5	4
Humerus.....	4	3
Scapula.....	2	2
Clavicle.....	1	1
Tibia.....	1	1

to the skeleton. In 80 per cent. (thirty-six cases) they were complicated by metastases to other parts of the body. In ten the skeletal metastases were followed by pulmonary and in ten others by cutaneous invasion. The relationship between the time of onset of skeletal and other metastases could not be determined in the remaining cases. The regional distribution of the first localization in the forty-five cases occurring in the pre-terminal stage is given in Table IV.

TABLE IV

First Localization in the Skeleton of Cases in the Pre-Terminal Stage, 45 Cases

Region	Per cent.	No. of Cases
Lumbo-sacral spine.....	39	17
Femur.....	18	8 { heterolateral, 7 homolateral, 1
Pelvis.....	16	7
Skull.....	8	4
Dorsal spine.....	7	3
Ribs.....	4	2
Scapula.....	4	2 { homolateral, 1 heterolateral, 1
Humerus.....	2	1 heterolateral

The anatomical distribution of metastases as given in Table IV corresponds to the finding of Lee,²¹ Semken,³⁰ and others, and differs somewhat from that quoted by Handley,¹³ and more recently by Carnett and Howell.³ While the figures on the frequency of involvement of the sternum and ribs quoted by Handley are probably nearer the truth than those given here, metastases to the lumbosacral spine, pelvis, and femur, surely occur more often than it would appear from the tables of this author. The discrepancy may be due to the fact that the criterion for localization of skeletal metastases in this series was pain and later a positive röntgenogram, whereas Handley's statistics are based on autopsy findings. It is well known that röntgenographs of metastases in the sternum and the adjacent portion of the ribs are rarely satisfactory.

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Histological Grading of Malignancy and Its Bearing on the Survival Period Following Discovery of the Tumor, the Metastases, and the Time Interval between These.—The microscopic structure of the primary tumor, or the metastases or both were investigated and an attempt was made in fifty-seven cases of skeletal metastases to grade the tumor according to the histological evidence of malignancy without reference to the clinical history. Variation in size and staining qualities of the cells and nuclei, frequency of mitotic figures, secretion vacuoles, glandular differentiation, connective tissue reaction, round-cell infiltration, and necrosis were studied. The order of importance of these factors in determining the degree of malignancy, is that just given. Grouping into Grade I and III was comparatively easy. Grouping of cases into Grade II on the other hand was difficult, as the histological characteristics in many cases approached either Grade I or III. This is illustrated in the following case.

B.G., with a primary inoperable carcinoma of the left breast, had a biopsy done and three years later died of broncho-pneumonia. The histological picture of the original tumor showed extreme variation in the size and staining qualities of cells and nuclei, two to three mitotic figures per high power microscopic field, no secretion vacuoles or attempt at glandular differentiation. Specimens obtained at post-mortem examination from skull, dura, brain and adrenals, on the other hand, showed slight to moderate variation in the size and staining qualities of cells, practically no mitotic figures, no secretion vacuoles, but a slight attempt at glandular differentiation. Our classification based on sections of the original tumor would have been Grade III, on sections from the autopsy material, Grade I. After seeing both we grouped the case as belonging to Grade II.

Of the fifty-seven cases twenty-six were thus classed in Grade I, twenty-six in Grade II, and five in Grade III. While inaccuracies in grading occurred, the general clinical value of this histological grading is supported by a study of the survival period after the discovery of the tumor as illustrated in Table V. It is interesting to note that five cases of Grade I with marked

TABLE V
Survival Period According to Histological Grading, 57 Cases

Grade	No. of Cases	Average duration of life in months
I.....	26	50.2
II.....	26	23.5
III.....	5	17.3

glandular differentiation had an average survival period of 71.1 months as compared to an average survival period of forty-five months for the twenty-one other cases which did not show this histologic characteristic.

Cases with marked connective tissue reaction (scirrhous cancer) showed somewhat increased survival periods for Class II and III, not for Class I. The significance of this finding may be questioned.

There were thirty-nine cases in which a radical amputation of the breast was done and six non-operated cases which could be graded according to the histological evidence of malignancy. The survival period varied with the histological grading and appeared to be somewhat shorter in the non-operated

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TABLE VI

Survival Period in Cases with Marked Connective Tissue Reaction, 16 Cases

Group	No. of Cases	Survival period in months
I.....	6	49.4
II.....	8	32.3
III.....	2	20

series. However, definite conclusions cannot be drawn on this last question on account of the marked numerical divergence of the two series. It might be interesting to mention, that the only three patients of the radically operated Grade I group that survived a year or less after the tumor was noted, were patients who showed pain and tenderness in bones before the operation, and post-operatively showed röntgenographic evidences of skeletal metastases. Whether this is a coincidence in patients operated upon when they were nearing their terminal stage, or whether the operative interference so lowered their resistance as to accelerate the approach of death offers interesting material for speculation.

TABLE VII

Duration of Life Arranged According to Histological Grading—46 Cases

Group	Cases with radical amputation of the breast		Non-operated cases	
	No. of cases	Survival period discovery of tumor to death (months)	No. of cases	Survival period discovery of tumor to death (months)
I.....	22	53.6	1	30
II.....	14	41.2	4	27.7
III.....	3	20	2	13.5

The influence on the survival period of the pre-operative duration of a palpable tumor in cases subjected to radical amputation of the breast was studied, but no definite conclusions could be arrived at, perhaps on account of lack of sufficient material. It seemed however that patients in whom the rate of growth of the tumor was slow²³ and who therefore visited the surgeon and were operated upon late did better than those in whom the rate of growth was rapid, caused discomfort and who were operated upon earlier. This in no way affects the advisability of early operation, but is the probable explanation of this unexpected finding. For instance, in three Grade III cases a radical mastectomy had been performed three months after the tumor was noted. The average survival period in these was only seventeen and one-third months. On the other hand in four cases of Grade I in whom the tumor had been noted for more than a year prior to the time of mastectomy the survival period was 47.6 months.

Our data was insufficient to form conclusions as to the possible influence of castration on the occurrence of skeletal metastases.

The time interval between the discovery of the primary breast tumor and

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TABLE VIII

Interval Between Discovery of Tumor and Onset of Skeletal Metastases—43 Cases

Group	Radically operated cases		Non-operated cases	
	No. of cases	Interval between discovery of tumor and onset of metast. (months)	No. of cases	Interval between discovery of tumor and onset of metast. (months)
I.....	19	46.5	1	29
II.....	14	29.1	4	21.1
III.....	3	10	2	6

the onset of symptoms of skeletal metastases as seen from Table VIII also seem to depend greatly on the histological grading of the tumor.

Survival after the onset of skeletal metastases varied from three months to four years and eight months. The combined terminal and pre-terminal, and then the latter alone were studied and graded histologically in Tables IX and X.

TABLE IX

Survival After Onset of Skeletal Metastases, 50 Cases

Grade	No. of Cases	Survival period in months
I.....	23	15.1
II.....	22	8
III.....	5	9

TABLE X

Survival of Pre-Terminal Cases After Onset of Skeletal Metastases, 32 Cases

Grade	No. of Cases	Survival period
I.....	15	19.7
II.....	13	16.2
III.....	4	10

The slightly longer survival period in the pre-terminal group as compared with the general group is naturally what one would expect.

Clinical Symptomatology of Metastases to the Skeleton.—Pain^{11, 24} and less frequently bony tenderness on direct pressure or percussion are usually the first symptoms of invasion of the skeletal system by metastases from cancer of the breast. In 75 per cent. *i.e.*, sixty-one of the eighty-one cases, attention was drawn to the presence of bony metastases through the fact that the patient complained of localized pain. This was usually at the site of the metastases, occasionally, however, over the area of distribution of the nerve immediately adjacent to the metastases. In 17 per cent. (fourteen cases) pain occurred at about the same time as röntgenographic corroboration was obtained and in only 7 per cent. (six cases) were metastases discovered incidentally when röntgenographs were made as a routine measure, the patient not complaining of any pain. In nine cases it was possible to follow the gradual appearance of definite röntgenographic evidence of skeletal metastases in places where the patient complained of pain from one-half to twelve months

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prior to positive röntgenograms. In these cases röntgenographs were made at frequent intervals until they became positive. In six of the cases the skeletal metastasis was the first point of localization; in three, involvement of other parts of the skeletal system had been diagnosed röntgenographically and attention to the new invasion was drawn by the patient's complaints. A table of the nine cases follows:

Interval between onset of pain and positive Röntgenographs	Clinical symptoms	Röntgenographs
½ mo.	F. H.—Severe pain sternal end of left clavicle 18½ months after discovery of tumor.	18½ mos. P.T.* Clavicles negative. 19 mos. P.T. Path. fracture 2" from sternal end of left clavicle.
3½ mos.	A. B.—When tumor discovered, pain in lumbar and sacral regions radiating anteriorly. Pain continued following operation 2 mos. later.	2 mos. P.T. Lumbar spine negative. 3½ mos. P.T. Slight narrowing of body of 1st L.V. Small area of bone absorption in left wing of sacrum.
3 mos.	C. T.—14 mos. P.T. Pain and tenderness 2nd left rib anteriorly.	14 mos. P.T. Chest and shoulders negative. 19 mos. P.T. Metastases 6, 7th right ribs 7th left rib. 22 mos. P.T. Metastases in practically all the ribs.
5 mos.	R. K.—7 mos. P.T. Pain in left hip and crest of ilium. 9 mos. P.T. Tenderness in lumbar spine and left hip. 12 mos. P.T. Pain in left hip radiating to ankles, right hip and also right shoulder.	9 mos. P.T. Pelvis and upper third of femora negative. 12 mos. P.T. Small area of rarefaction in left pubic bone. Femora negative. 17 mos. P.T. Area of bone destruction and sclerosis in descending ramus of right ischium. Metastases in left os and descending ramus of left pubis.
6 mos.	H. F.—9 yrs. 9 mos. P.T. Pain right foot. Pain in right foot persisted.	9 yrs. 9 mos. P.T. Right foot negative. 10 yrs. 3 mos. P.T. Metastasis to right cuneiform bone.
7 mos.	R. T.—16 mos. P.T. Severe pain in dorsal region.	16 mos. P.T. Dorsal region negative. 23 mos. P.T. Multiple metastases in dorsal vertebræ.
7 mos.	S.—27 mos. P.O. Pain in both shoulders radiating down the arms. Pain persisted.	27 mos. P.O. Shoulders negative on numerous chest films taken before and following this date. 34 mos. P.O. Metastasis to head of right humerus.
8 mos.	R. K.—34 mos. P.T. Pain right leg. 36 mos. P.T. Pain and tenderness right lower tibia. 38 mos. P.T. Marked tenderness over tibia. 42 mos. P.T. Swelling and tenderness right ankle.	34 mos. P.T. Right leg and foot negative. 37 mos. P.T. Right ankle and leg negative. 39 mos. P.T. Right tibia negative. 42 mos. P.T. Few areas of bone destruction lower end of right tibia and fibula; röntgenographic appearance suggestive of metastases.

* P.T. after discovery of tumor; P.O. after operation.

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Interval between onset of pain and positive Röntgenographs	Clinical symptoms	Röntgenographs
11 mos.	C. T.—16 mos. P.T. Pain and tenderness both scapulæ.	16 mos. P.T. Shoulders negative. 19 and 22 mos. P.T. Chest X-rayed for ribs—negative. 28 mos. P.T. Multiple metastases in scapulæ.
12 mos.	R. B.—16 mos. P.T. Onset of pain and bony tenderness right ribs.	10 to 16 mos. P.T. Röntgenographs of chest during this period were negative for rib metastases. 22 mos. P.T. Metastasis to 2nd right rib.
12 mos.	R. S.—7 mos. P.T. Pain in back. 11 mos. P.T. Radical mastectomy. Pain in back persisted post-operatively. 18 mos. P.T. Pain in back became very severe and started to radiate down the thighs.	11 mos. P.T. Lumbo-dorsal spine negative. 13½ mos. P.T. Pelvis negative. 19 mos. P.T. Extensive metastases to 4th and 5th lumbar vertebræ 21 mos. P.T. Metastases to all lumbar vertebræ and pelvis.

Pain apparently is earliest and most pronounced where pressure due to natural body weight or muscular tension is greatest. Thus, for instance, pain due to invasion of the lumbar spine or sacro-iliac region is usually present early, whereas pain due to invasion of the vault of the skull is commonly not complained of until late in the course of this metastasis, when it has either reached a considerable size or is producing increased intra-cranial pressure. While pain and bony tenderness usually indicate the presence of skeletal metastases, this diagnosis can only be made on the basis of röntgenographic evidence or microscopical examination. Indirect symptoms of skeletal metastases such as cachexia and unusual blood findings such as mentioned by Piney²⁷ were not carefully studied in this series. It was found, however, that cachexia did not seem to be an important symptom except in the terminal stage of the disease.

Röntgenographic Corroboration.—Before the advent of recent improvements in röntgenographic technic² and the recognition of the frequency of skeletal metastases, many cases were missed. At present, however, many more metastases are recognized. The röntgenographic characteristics of skeletal metastases from cancer of the breast closely correspond to the pathological findings. The lesions may be circumscribed or diffusely infiltrating. They are generally of the osteoclastic type (77 per cent. in this series) and less frequently a mixture of osteoclastic and osteoblastic types with the one or the other predominating (23 per cent. in this series). In some cases the amount of new bone laid down is so great that the areas involved become very dense and röntgenographically give an almost ivory-like appearance. The extensive, infiltrating types of skeletal metastases are the ones most likely to show osteosclerosis. Small localized areas of bone sclerosis are

occasionally seen especially near the sacro-iliac joint. These areas may be benign, but require repeated röntgenographic check-up in order to avoid overlooking the development of early metastases. The same caution should be exercised in interpreting the significance of röntgenographic evidence of spondylitis. This may often mask an early metastasis.

Pathological Fractures.—Pathological fractures of one or more of the long or flat bones were encountered in 26 per cent. of the cases (twenty-one of eighty-one). They occurred only in the terminal stage of the disease. Fractures were observed in the femur (nine cases), humerus (nine cases), ribs (two cases), and clavicle (one case). The fractures of the ribs were probably much more numerous, but were missed on account of the difficulty of the röntgenographic diagnosis of rib involvement.

Effect of Radiotherapy.—In considering the possible benefits from radiotherapy in skeletal metastases it should be remembered that the greater number of patients were admitted to the Radiotherapy Department of Montefiore Hospital during the terminal stage of the disease. In only thirty-one of the eighty-one cases was it possible to evaluate the results of radiotherapy. The number of treated cases in each of the histological grades was insufficient to permit any definite conclusion on this question. The metastases were usually so widespread that only mild palliation was attempted. In three cases the metastases seemed to be localized to a single bone. Two of these improved in spite of the fact that they were in the terminal stage of the disease. In nineteen cases treated during the terminal stage of the disease, ten showed clinical improvement and nine remained unimproved. Of twelve cases treated in the pre-terminal stage, all were markedly improved by therapy. The duration of improvement varied from a few weeks to three years. It was manifested in relief of pain within twenty-four to forty-eight hours after the first X-ray treatment; and there was progressive improvement in many cases. The clinical improvement was at times striking. Thus we had two patients that were admitted as apparently hopeless and moribund, who were able to leave the hospital walking after they had received a series of X-ray treatments. They remained clinically well for twenty-seven and thirty-six months respectively. One of them, a milliner, was able to follow her regular occupation during a period of over three years.

Bone sclerosis following X-ray therapy occurred in fourteen of thirty-one cases. In ten this had not been present prior to irradiation, in four the metastases were osteoblastic before irradiation and the bone sclerosis was somewhat increased in density following the treatment. The dosage apparently was not the determining factor in producing the improvement. Most of the cases were treated with X-rays with the following factors: 200 KV, 0.5 millimetre copper filter, 50 centimetre target skin distance, and moderately sized fields. A few cases were treated with radium packs at a distance of two to three centimetres (this was done before our association with the department). A "series" of treatments consisted of the total amount of

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radiation given within a period of about two months. The administration of more than two erythema doses to the skin over one area in a series was considered a large dose; one or two erythema doses as a moderate; and less than one erythema dose as a small dose. It was found that those cases which improved did so with small or moderate amount of irradiation. In twenty-one cases in which clinical improvement occurred following the treatment with X-ray and radium, the dosage was small in seven, moderate in thirteen, and large only in one case.

Radiotherapy of pathological fractures could be evaluated in seven cases. Four fractures did not unite. Three of these had very little and one a large amount of irradiation. A fracture of the middle third of the humerus showed marked callus formation after two small X-ray treatments. Bone sclerosis, but no union, followed the administration of moderate amounts of X-ray treatment to a fracture of the surgical neck of the femur. Complete bony union of a fracture of the left clavicle was noted following very small radiation doses from a 3-centimetre radium pack. Union of pathological fractures in several cases of cancer of the breast has been observed without any treatment (Harold Neuhof, personal communication).

A remarkable case not included in this series should be mentioned in this connection. It is a case of generalized skeletal metastases from a carcinoma of the breast with involvement of the skull, the spine, the pelvis, *etc.* The various skeletal metastases were irradiated with small doses of X-rays and improvement followed. The skull was not exposed to X-rays, yet comparison röntgenographs showed marked diminution in the size and number of the osteoclastic metastases in the skull. Evidently something more than local X-ray effect took place in this case.

Metastases to the Central Nervous System.—It was mentioned in the beginning of this paper that clinical differentiation of compression, extension, and metastases in the central nervous system from cancer of the breast is difficult if not impossible. Since only nine of the twenty-five cases suspected of brain metastases and four of the thirteen cases diagnosed as spinal-cord metastases were examined post-mortem, our figures as to frequency of occurrence of metastases into the central nervous system are not quite accurate. As a matter of fact, it may be questioned whether true metastases occurred in the spinal cord or whether all cases with cord symptoms were either compression by, or extension from a metastatic focus in the corresponding vertebrae. Symptoms of metastases to the central nervous system occurred in nearly 21 per cent. of the 168 cases investigated. Sixty-eight per cent. of the cases (seventeen of eighty-one) with neurologic evidence of brain involvement also showed positive röntgenographs of skull metastases. *Vice versa*, 68 per cent. of the patients with röntgenographic evidences of metastases to the skull also showed definite symptoms of brain invasion.

The symptoms of the onset of the brain invasion varied. They can be divided into three groups:

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- A. Cases showing signs of gradually increasing intracranial pressure (three cases).
- B. Cases with signs of increasing intracranial pressure and localizing neurologic signs of cerebral, cerebellar or brain stem involvement (eleven cases).
- C. Cases showing neurologic signs of cerebral, cerebellar and brain stem invasion without increased intracranial pressure (ten cases).

In 68 per cent. (seventeen of twenty-five) of the brain metastases and in 70 per cent. (nine of thirteen) of spinal-cord cases, the involvement occurred during the terminal stage of the disease. The survival period after the appearance of neurologic evidence of involvement in the eight pre-terminal brain cases varied from seven to twenty months, and in the four cord cases from five to thirty-one months. The effect of radiotherapy could be evaluated in five pre-terminal brain cases and in three pre-terminal cord cases. Three of the brain cases had shown early signs of increasing intracranial pressure. In one case, as a result of moderate X-ray therapy, headache disappeared for a period of four months, then re-appeared and was again relieved for a short time, then the patient succumbed to brain stem involvement. In another, headache was relieved for six months then recurred as a terminal feature. At autopsy extensive involvement of the dura without invasion of the brain was found. In the third case headache, vomiting, and convulsions of the right upper extremity disappeared following a small radium application and little X-ray treatment to the opposite side of the brain. The survival period in these three cases after the onset of clinical evidence of brain metastases were eleven, eighteen, and twenty months respectively. It is noteworthy that the generalized skeletal metastases in these patients also responded well to the X-ray therapy which they received. Of the two cases which gave neurologic signs of localized involvement of the brain, one improved following a small radium pack, while no improvement was noted in the other, after apparently well-placed, moderate X-ray therapy. Several other cases are not quoted in detail as they occurred in the terminal stage. They showed temporary regressions of headache, and diplopia, and disappearance of facial palsy for periods varying from a few weeks to three months. Of the three cord cases, two showed definite relief of pain from moderate X-ray dosage. No beneficial effect was seen in the third case.

SUMMARY

One hundred and sixty-eight cases of metastases to various body systems from carcinoma of the breast were studied from the time of discovery of the tumor to the time of death. Forty-eight per cent. had skeletal metastases, 15 per cent. showed brain metastases, and 8.7 per cent. spinal cord-involvement.

Of the eighty-five cases of metastases to the skeleton and central nervous system thirty-two were examined post-mortem, sixty-seven were corroborated histologically, and sixty were graded according to the histological evidence of

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malignancy into three groups: Grade I or least malignant, Grade II or moderately malignant, Grade III or most malignant.

It was found that three time factors varied in direct relation with this grading: *a*, the time interval between the discovery of the tumor and the onset of symptoms of skeletal metastases; *b*, the survival period after discovery of the tumor; and *c*, after symptoms of skeletal metastases. These three periods were markedly shortened with increasing malignancy; thus the average interval between the discovery of the tumor and the onset of metastases was 46.5 months for Grade I, 29.1 months for Grade II, and 10 months for Grade III. The survival period after the discovery of the tumor for cases in Grade I was 50.2 months, Grade II 23.5 months, and Grade III 17.3 months. The survival period of pre-terminal cases after the onset of skeletal metastases was 19.7 months for cases in Grade I, 16.2 months for those of Grade II, and 10 months for those of Grade III. The survival of cases with marked glandular differentiation was somewhat longer than those which did not show this characteristic.

The term of the patient's life following the discovery of the tumor was divided into two periods, a terminal period, that is the last third or in cases lasting more than three years, the last year of life, and pre-terminal or earlier period; 55 per cent. of the skeletal metastases occurred in the pre-terminal period.

Age apparently had no influence upon the survival period and most cases occurred between the ages of forty and fifty.

The primary tumor arose in the right breast in forty-three and the left breast in thirty-eight cases.

Of forty-five cases occurring in the pre-terminal stage, the skeleton was the primary localization in 82 per cent. However in only 16 per cent. did it remain limited to the skeletal system. In the rest it was associated with metastases to other parts of the body.

The most frequent localization in the skeleton of the pre-terminal cases was the lumbo-sacral spine, the femur, pelvis, dorsal spine, skull, ribs, scapula, and humerus, in the order mentioned.

Pain was the first sign to call attention to skeletal metastases in 75 per cent. of the cases. The time interval between the first complaint of pain and the appearance of definite röntgenologic evidence of skeletal metastases was followed carefully in nine cases. It was found to vary from a few weeks to one year.

Pathologic fractures occurred as a terminal manifestation of the disease and were encountered in 26 per cent. of the cases. Of seven treated pathologic fractures only one united after a radium application.

X-ray and radium therapy were very useful agents in control of pain. They caused diminution and at times marked temporary regression of the clinical and röntgenographic signs of skeletal metastases. Clinical improvement started twenty-four or forty-eight hours after the first treatment and

lasted from a few weeks to three years. Moderate dosage seemed to be sufficient and sclerosis of the radiated bone was observed in several cases.

Clinical signs suggesting metastases to the central nervous system occurred in 21 per cent. of the one hundred and sixty-eight cases investigated and were usually a terminal manifestation. Clinical differentiation between compression, extension and true metastases into the central nervous system was impossible. Sixty-eight per cent. of the cases diagnosed as brain involvement showed positive röntgenograms of skull metastases and all cases diagnosed as spinal-cord metastases showed röntgenographic evidence of a preceding metastasis to the lumbar vertebra at the same level. In a few cases temporary regression of signs of increased intracranial pressure and localized brain involvement occurred following moderate dosage of radiotherapy.

CONCLUSIONS

The prognosis of skeletal metastases from cancer of the breast varies with the histological character of the primary tumor or its metastases. This influences the survival period after the discovery of the tumor and after the onset of the metastases, and has a bearing upon the time interval between the discovery of the tumor and the onset of skeletal metastases.

Pain usually precedes positive röntgenographs of skeletal metastases and is the most important symptom of skeletal invasion.

Clinical signs suggesting metastases to the central nervous system from cancer of the breast occurred in about one-fifth of the cases investigated. In more than half of the brain cases there were associated metastases in the skull and in all of the spinal cord cases there were metastases in the corresponding vertebrae.

Radiotherapy relieves pain in a great number of cases of skeletal metastases. In a few cases of skeletal metastases it produced a remarkable temporary regression and in a few cases of invasion of the central nervous system it also caused palliation.

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PAPILLOMA OF THE DUODENUM

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TUMORS of the duodenum are of such relatively infrequent occurrence as to justify the placing on record of cases as they occur, although the literature of the subject is beginning to assume considerable proportions. Perhaps the most exhaustive articles to date are those of Golden, in the *American Journal of Roentgenology and Radium Therapy*, and Eliason, Pendergrass, and Wright, in the same publication. Anyone interested in the literature on the subject should consult these comprehensive résumés.

Almost every type of benign tumor encountered elsewhere in the intestinal tract may be found in the duodenum. Instances of adenoma, calcified submucosal fibroma, adenoma of Brunner's glands, myoma, polypoid thickenings, hæmangio-endothelioma, lymphangio-endothelioma, *etc.*, are recorded in the literature.

It is worthy of note that in a considerable number of cases, tumors of the duodenum were associated with pathological conditions elsewhere in the intestinal tract—multiple polyposis, carcinoma, cholelithiasis, *etc.* Tumors of the duodenum seem to be confined to no particular age; reported cases range from infants of a few days to individuals of over seventy years. There seems to be no particular pathognomonic picture associated with their presence. They give rise, as a rule, to symptoms that suggest more strongly, perhaps, than anything else, duodenal or gastric ulcer or carcinoma. Hæmorrhage, either macroscopic or microscopic, sometimes very severe, is common. Pyloric obstruction, more or less pronounced, is often present. The usual diagnosis is a provisional one of duodenal ulcer. In general, though, there seems to be less actual pain than one is accustomed to associate with true ulcer. In a few cases, the diagnosis has been made by Röntgen-ray examination, usually with the aid of the fluoroscope. It is based upon the demonstration of a characteristic filling defect in the shadow of the barium-filled duodenal bulb. In our case, the diagnosis was definitely made by Dr. Thomas R. Brown, with the aid of the fluoroscope, which diagnosis was later confirmed by plates taken by Dr. Charles A. Waters, whose plates, together with his interpretation of them, are appended.

In differentiating these cases, Golden attaches considerable importance to the presence or absence of a six-hour gastric retention. He states that "in the presence of a filling defect in the duodenal bulb, suggesting non-malignant tumor, a six-hour gastric retention may be considered as evidence in favor of a growth arising in the stomach and prolapsing into the duodenum, and the absence of such a retention as indicative of a growth arising in the duodenum itself." In our case there was no retention, the stomach emptying

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within normal limits. In addition to their comparative rarity, the especial interest in these cases attaches to the matter of diagnosis and treatment, especially in view of the ever-present tendency of papillomatous growths of the mucosa to degenerate into carcinoma.

The chief reason for reporting this case is to emphasize the fact that this is one other condition that must be borne in mind in making a diagnosis in the case of gastric or duodenal trouble. It emphasizes, too, the necessity for a very careful fluoroscopic study of all such cases. While it may not be possible in every case to make the diagnosis, certainly the fact that a correct diagnosis has been made in a certain percentage of the cases reported shows that the attempt should be made.

Where the growth has a small, well-defined pedicle, ligation and excision of the entire thickness of the mucosa are probably all that is necessary. One, however, should never forget the possibility of malignant degeneration. The specimen in our case showed that it had already begun, although not recognized until examination of the microscopical slides showed its presence, so that nothing short of resection would have offered a cure.

The outcome in our case was extremely unfortunate. It represents another of those calamities of surgery of which Paget wrote so eloquently many years ago and which, in spite of every precaution, happen now and then to every operating surgeon of experience.

REPORT OF CASE.—(Dr. Thomas R. Brown.) Patient, male, aged sixty-eight years, was admitted to the Union Memorial Hospital November 23, 1929, on account of pain in the epigastrium when stomach was empty. His illness was of six months' duration. Previous to that time, had no digestive trouble. Bowels regular. Trouble began as epigastric discomfort, most pronounced during the forenoon; not much in evidence in the afternoon or at night. Sometimes pain was relieved by an alkali or something to eat; no nausea or vomiting; no gross blood in the stools; no jaundice.

For the past two months symptoms had been aggravated, with very little intermission. With reduction of the amount of food ingested, patient felt more comfortable. This was followed by moderate loss of weight.

His past history presented nothing of interest.

Examination revealed a well-nourished man. Mucous membranes rather pale; pupils somewhat irregular; react normally to light; tongue slightly coated; teeth negative. No palpable glandular enlargement. Heart and lungs negative. Blood-pressure 150/96. Abdomen showed liver with upper limit normal; edge palpable two fingers' breadth below costal margin; spastic sigmoid slightly tender. Nothing else made out by palpation. Rectal examination negative.

The test meal showed an achlorhydria—free acid 0; total 8. Urine was negative. The one specimen of stool examined showed occult blood present; no parasites. The hæmoglobin was 92 per cent.; the white blood cells, 9,400. Blood Wassermann was negative.

The fluoroscopic studies of the gastro-intestinal tract showed a stomach normal in tone and function, fish-hook in type, absolutely normal in contour. The duodenal cap was extremely interesting; irregular, not filled in the centre, but filled as a shell around the periphery. This same picture was seen in repeated examinations. The duodenum was moderately dilated but could never be filled in any position in which the patient was put.

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From the history, which was somewhat suggestive of duodenal ulcer, from the achlorhydria and from the fluoroscopic studies, the diagnosis was made of a papillomatous growth of the duodenum, and operation was advised.

According to the X-ray report made by Dr. Charles A. Waters "the pylorus seems to be all right, but, as the barium goes through the duodenum, it spreads out in a fan-shaped manner, as though it were encircling a mass. The marginal contours of the duodenal cap seem to be perfectly normal. A series of films showed a definitely enlarged duodenal cap with a smooth contour, but with a very multilocular type filling defect, which seems to be inside the cap.

Impression.—There is no doubt that there is a lesion present, but the etiological factors are certainly very confusing from an X-ray point of view. It would seem almost certain that a neoplasm should be considered. In any other part of the intestinal tract, this type of filling defect would warrant a diagnosis of papilloma or polyposis.



FIG. 1.—Film of the stomach and duodenum immediately after the ingestion of the barium meal showing the smooth contour of the duodenal cap with its multilocular, vacuolated appearance within the duodenum and the depression of the pyloric sphincter by the papilloma acting as a ball valve.

Comment.—In studying Fig. 1, one can see at a glance that the filling defect in the duodenum is a very unusual one, and that a diagnosis such as papilloma from this film is not such a hazardous guess. However, in neither the fluoroscopic examination by Doctor Brown and myself nor in a considerable number of films was this visualized with any such clearness as shown in Fig. 1. This fact is mentioned in order to show the necessity of making films of fine detail in gastro-intestinal examinations, in addition to the fluoroscopic examinations."

OPERATION.—(Dr. J. M. T. Finney). November 25, 1929. Gas-ether anaesthesia; high right rectus incision. Examination of the stomach and duodenum revealed a soft mass about the size of an olive in the lumen of the first part of the duodenum. The anterior duodenal wall was incised over this mass, exposing a lobulated papillomatous tumor with a rather broad base. It was felt that if the tumor were excised, considerable

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narrowing of the lumen of the duodenum would inevitably result. Resection was, therefore, decided upon.

The typical operation was performed, removing terminal 2 inches of stomach, pylorus and upper $1\frac{1}{2}$ inches of duodenum, followed by a Polya anastomosis. No difficulty of any kind was encountered.

The patient stood the operation well, but the evening temperature showed considerable elevation. The temperature continued to rise, in spite of anything that could be done. The pulse became accelerated with the rise of temperature, finally reaching, on the third day, temperature 104° , pulse 140. There was evidence of a generalized peritonitis, and, on the fourth day, the patient died with every evidence of septic infection.

Autopsy.—Upon reopening the abdominal incision, a rather large pocket of pus was found in the abdominal wall, not communicating with the peritoneal cavity. The peritoneum showed mild, early, generalized peritonitis. About 300 cubic centimetres of slightly blood-tinged fluid in the abdominal cavity. There were two or three definite, small, localized abscesses present, one about the upper margin of the anastomosis—the largest contained 200 cubic centimetres of thick, creamy pus, apparently arising about the stump of the duodenum. The suture line of the anastomosis was everywhere tight, except at the upper angle, where there was a questionable leak. Stump of duodenum seemed tight. Cultures showed streptococcus and bacillus coli.

Diagnosis.—Acute generalized peritonitis with localized abscesses.

Comment.—This was one of four cases, all operated upon within a few days, with the same technic, assistants and material, all of which cases showed a similar post-operative picture. Three of the four cases died. There had been no infections in the operating room previously; there were none subsequently. All operating was at once stopped, and an exhaustive study of the entire operating technic, staff, materials, etc., was made by Dr. W. W. Ford, of the Bacteriological Department of the Johns Hopkins University, all of which proved negative in every way, except for a particular brand of catgut, which had been used in these cases, and which showed repeated cultures of an anaerobic diptheroid.

This experience, which was most unfortunate, shows how important it is to make frequent tests of everything that comes into contact with an operative case. The firm making this particular catgut was at once notified of the findings. There has been no trouble since.

PATHOLOGICAL REPORT.—(Dr. W. G. MacCallum.) "The specimen consists of the pylorus of the stomach and the first part of the duodenum, which contains a polypoid



FIG. 2.—Photograph of the specimen after removal.

Wm. P. Didusch 1929

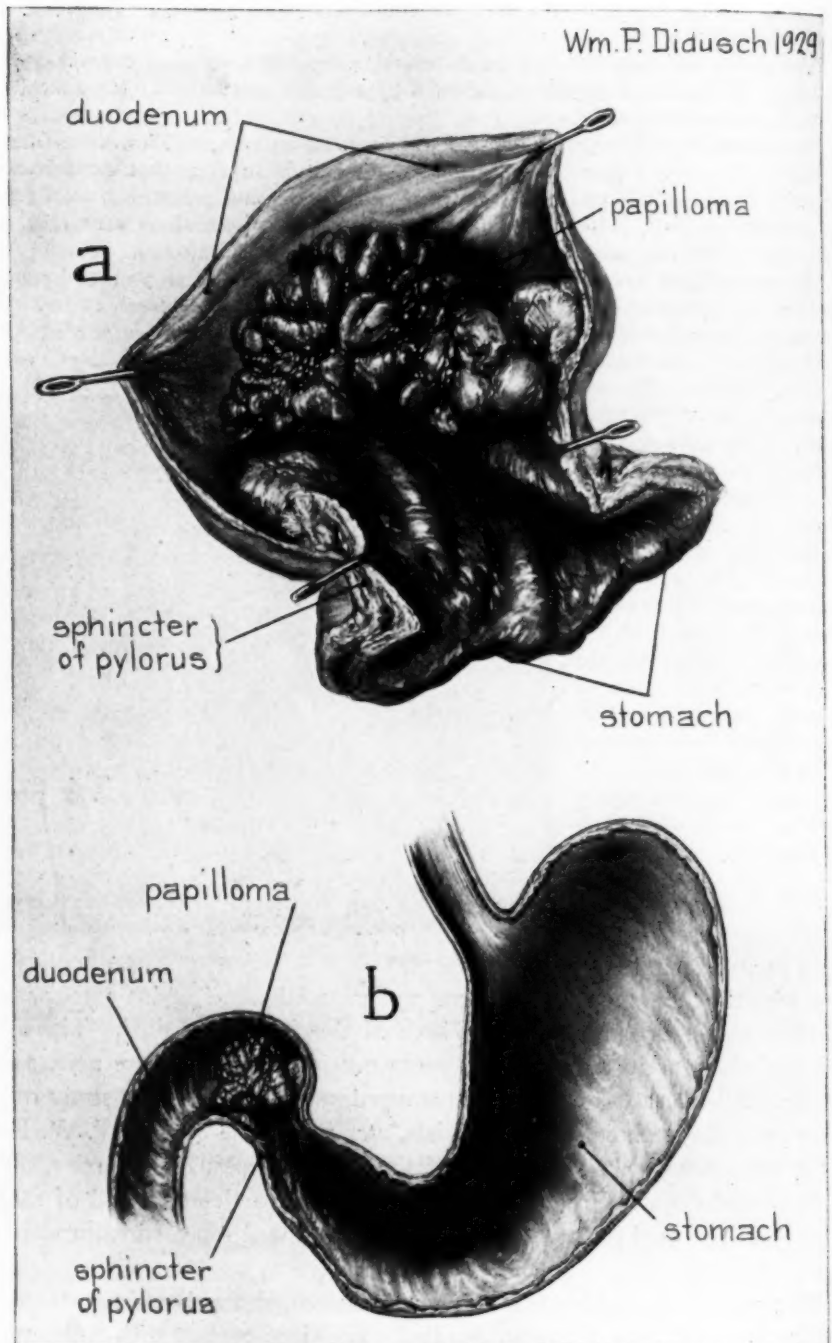


FIG. 3.—a.—Shows the arrangement of the papilloma in the duodenum.
b.—Diagrammatic sketch showing the relative size and location of the papilloma with reference to the pyloro-duodenal junction.

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growth extending into the lumen. There is a fold of tissue where the pylorus is usually seen, and below this point there is duodenum. However, at another point in the circum-

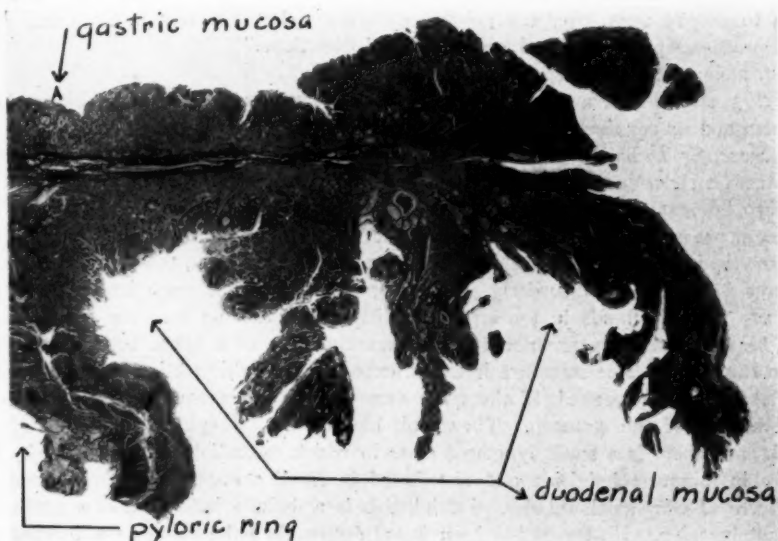


FIG. 4.—Microphotograph showing the papilloma and the extraordinary formation of the polypoid epithelium.

ference, at the same level, the mucosa of the stomach is seen to extend downward and up on to the polyp, so that it would appear that the polyp is really derived from the

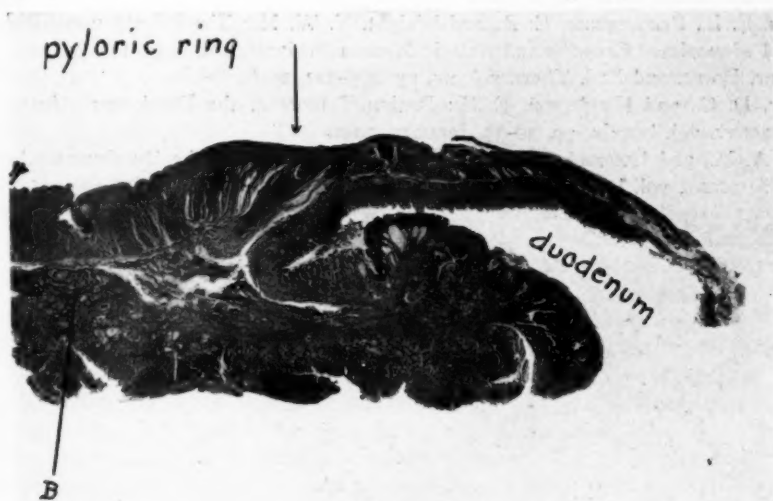


FIG. 5.—Microphotograph showing the pyloric sphincter and duodenum with invasion of the deeper layers of submucosa of the stomach.

stomach and has been dragged down to lie in the lumen of the first part of the duodenum. This may, however, not be borne out histologically.

"The polyp itself forms a mass measuring 4.5 centimetres from base to tip, and 5 centimetres in diameter in its outer portion. There are, however, other masses of the

same tissue which grow out from the base of the polyp in a more sessile manner and completely encircle the lumen just below the pylorus.

"On longitudinal section through the more pedunculated portion, the stomach mucosa is seen to extend down over the polyp, measuring 1-2 millimetres in thickness. Club-shaped processes project from the pedicle in all directions."

Fig. 2 shows the gross specimen after removal.

Fig. 3 shows a drawing, illustrating the arrangement of the papilloma in the duodenum and its relationship to the pylorus.

Microscopic Description.—"The sections taken longitudinally through this hanging, polypoid mass show gastric mucosa on one side, and duodenal mucosa on the other. Fig. 4 is a microphotograph of the longitudinal section through the pylorus and duodenum. The gastric mucosa at 'A' clearly shows an extraordinary formation of ramifying, glandular downgrowths in patches, scattered in the more normal mucosa. In the polyp, the epithelial structures become very disorderly, remaining gland-like, but very irregular in form. There are tubular glands in the stroma, which are drawn up into the polyp, but one cannot be sure that they are not due to tangential cuts of a space between two folds.

"In Fig. 5, the same structure is found, except that in this section the polyp is more sessile. At the point marked 'B' there are very definite downgrowths of epithelium into the submucosa of the stomach. They look like tubules of epithelium lying in lymph channels, and there is a small lymphoid mass in which epithelial cells are lodged. Here they are in minute subdivision and distributed in small groups in the lymph-node and in the form of very small tubules. I think this is a definite indication of a tendency to malignant invasion. No tumor has been found deeper than the submucosa, but there the invasion of lymphatics is extensive."

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CARCINOMA PERIGASTRODUODENALE

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TUMORS of the external coats of the stomach are not frequent and all are of the type of connective tissue sometimes mixed with epithelial proliferations. Among them sarcomata are most common and for the purposes of this paper only sarcomata and other tumors arising from external layers of the stomach and having an exogastric development will be considered later. Epithelial tumors growing exogastric are unknown to me.

Here is presented a case of epithelial tumor arising probably from the subserous stomach-duodenum coat and which for convenience I shall call carcinoma perigastroduodenale.

CASE HISTORY.—B. A., forty-three years of age. Nothing important in his family and in his personal history. In May, 1915, after a raid of Austrian destroyers against his native town on the sea and especially after an air bombing, he began to feel agitated, sleeping irregularly while he was compelled to work hard to change his home. In the beginning of August severe toothache prompted him to have a medical examination. He had already observed that his abdomen had grown rather hard on the right side, what he believed to be a faecal accumulation notwithstanding all his functions were regular. The doctor told him that it was a tumor and other doctors said the same afterwards. X-ray examination confirmed the diagnosis. I saw him November 10, 1915. He was rather thin and pale. Subjective symptoms were absent, except for some eructations after meals, and a sensation of drawing down from under the sternum when he was standing. Appetite, stomach and bowel functions normal. Physical examination of chest negative.

The abdomen showed a slight prominence on the right side of the mesogastrium reaching the median line mesially and almost the anterior axillary laterally. Palpation showed a mass of about 9 by 8 centimetres of irregular surface, hard, with an inferior lobulated margin, better limited than the superior one where from time to time one could perceive a soft swelling vanishing under the pressure of the hand. The mesial border was the less definite and while one could almost grasp the tumor externally and inferiorly and in part also above, it was impossible to do so on the medial side. The tumor was slightly movable with respiration and could be pushed freely from right to left and the contrary, but much less from up downwards or in the opposite direction. The most prominent part was dull on percussion; above and laterally the resonance was tympanitic. No pain during the examination.

X-ray report states: The stomach is pushed to the left, the great curvature has the shape of a sack and reaches a point three to four fingers under the transversal umbilical line. The shadow of the tumor corresponds to the pyloric portion of the stomach, which after 8½ hours is not completely emptied; there are no contractions. Movements imparted to the tumor are transmitted to the stomach. No mention is made about pylorus and duodenum conformation. The colon was regularly filled and without abnormalities. The diagnosis appeared evident—a tumor belonging to the stomach, but outside of it. It was uncertain whether it had grown directly from its outer coats, or, originating from some other structure outside of it, had developed toward the stomach and become attached to it. About its nature also nothing definite could be said as no sign was present which suggested the many existing possibilities. Certainly it was not

a cancer of stomach proper for the radiologist had not seen any sign of it; nor did the patient have symptoms pointing to such a tumor.

Formerly a case of an uncommon tumor of the stomach had been operated upon by me. It was a large tumor located in the middle of the greater curvature and extending down between the layers of the gastrocolic ligament and adhering to the transverse colon. The mucous coat of the stomach was ulcerated and for that reason the tumor was catalogued as stomach cancer with extrinsic development. It proved later, on reviewing the sections, that this was not so. But this case caused me to think that the one in discussion could be similar to that and consequently the diagnosis of cancer of stomach with extrinsic development was thought to be the most probable one.

Operation.—Ether narcosis. Longitudinal transrectal incision on the right. It was easy to lift the tumor out of the wound and to see that it was larger than it had appeared (Fig. 1). It belonged to the pyloroduodenal part of the stomach, of which the walls appeared normal. The pylorus and duodenum were pushed upwards and the latter also outwards, very considerably enlarged and stretched also in the length. The

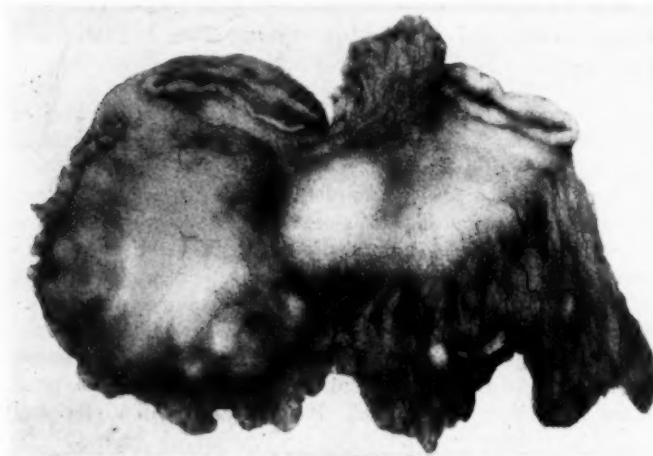


FIG. 1.—Perigastroduodenal carcinoma.



FIG. 2.—Sagittal section through duodenum and tumor.

lower pole of the tumor was adherent to the right portion of the transverse colon. The tumor was partially enclosed posteriorly in the gastrocolic ligament as if, originating from the stomach walls, it had pushed down and behind the layers of that ligament, being free from it in front.

The great omentum was ligated in portions under the growth, and after it had been made clear that the transverse colon was not involved, the tumor was separated from this; then a part of the great and small omentum was detached from the two curvatures, the stomach clamped and cut well above the antrum, was turned to the right and the duodenum made free for a few centimetres under the tumor and cut. The tumor was removed as Fig. 1 shows and the duodenum, stretched as it was, showed such a large stump that it could be united end to end to the stomach. As far as the inspection could ascertain, nothing abnormal was observed in the upper right abdomen. Recovery was uneventful.

The patient returned in April in a cachectic condition, showing a large liver metastasis, and died from it toward the end of April.

Anatomical Study of the Tumor.—Fig. 1—represents it almost in its natural size. It is a solid, rather hard mass, 10 by 8 by 7 centimetres. The surface and the contour

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is lobed, the color reddish, with brown hæmorrhagic spots and stripes. It is attached largely and firmly to the great curvature in proximity of the pylorus, and to the first portion of the duodenum which is greatly enlarged. The gastrocolic ligament lies partly behind the tumor, and the great omentum hangs down from its lateral and lower edge, so that a portion of the posterior surface is covered, while the anterior is free.



FIG. 3.—Frontal section of tumor. In (A), a thin normal pancreas layer.

Examination of the mucous coat of stomach and duodenum showed it to be movable or independent of the growth, and normal.

A sagittal section through duodenum and growth (Fig. 2), near the pylorus where the attachment seems closer, shows that the tumor has a thin capsule except above where it is fused with the duodenal wall whose layers are independent but for the serosa. Same result gave another section cardinal warts of the pylorus. The section



FIG. 4.—Parenchyma of the tumor.



FIG. 5.—Tubular formations on the left. In the middle an oral formation similar to an island. Note the abundance and structure of the connective tissue.

surface is yellowish gray with many small soft areas and spaces and with a large central cavity containing necrotic hæmorrhagic masses.

A frontal section of the tumor cut as in Fig. 3 shows better the relations of it with the duodenal walls. We see all the coats independent of the growth but in one part the outer muscular coat is involved, also the serous coat for a larger extension.

Here no capsule can be traced, also none farther posteriorly, where a thin layer of normal pancreas removed with the duodenum is almost fused with the growth. Microscopically the separation from the pancreas is evident.

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The capsule is made of very fine connective fibres, with thin, flat, elongated nuclei, disappearing in the most central layers; it is infiltrated above by the growth in the form of thin, oblong strands, apparently in vascular spaces. The tumor is almost uniformly necrotic, and it is possible to follow in it for a great distance a connective

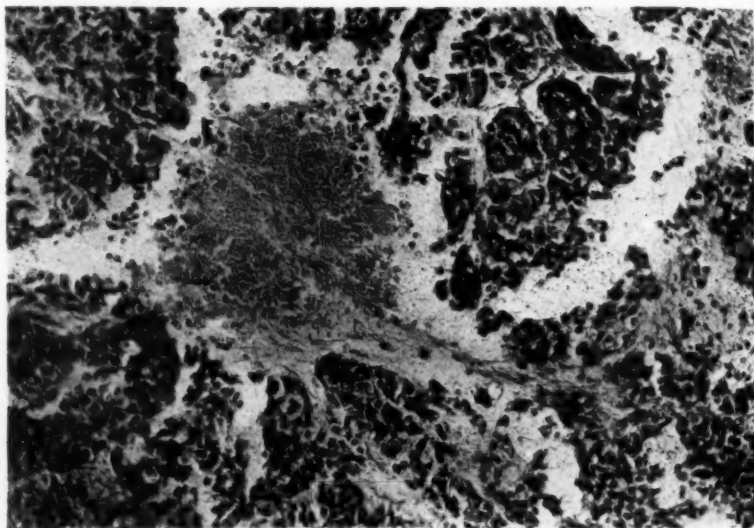


FIG. 6.—In the centre, a necrotic mass. All around lobule-like formations.

framework which, starting from the capsule, divides the tumor mass into large areas, and these again into smaller irregular ones.

The parenchyma of the tumor (Fig. 4), is arranged in oblong masses, which are divided by the connective framework into smaller portions, that is, into strands and

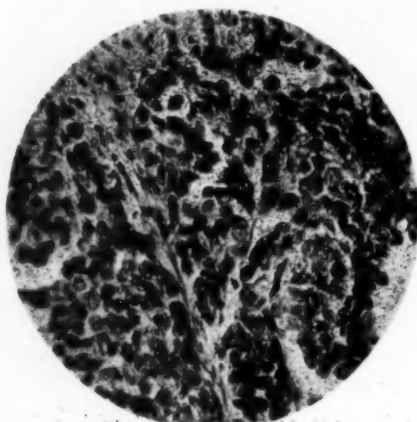


FIG. 7.—The cell structure of the tumor.



FIG. 8.—To show the extensive and various cellular degenerations.

columns of cells. These are resting peripherally on the fibres of the framework, while in their central parts appear hæmorrhagic and necrotic spots. Generally the solid columnar structure is the prevailing one, but in some parts cavities or lumina of different sizes are demonstrable, surrounded by one or more layers of cells, so that in these points the structure has an adenomatous appearance (Fig. 5). Here the connective

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stroma is abundant and largely cellular. In other parts the structure is more lobular (Fig. 6).

The cells of the tumor are of different forms and sizes. As the growth is mostly necrotic and the unfavorable vascular conditions are extensive, even in the best preserved parts there are degenerative changes of the cells of various character. This makes it difficult to describe a cellular type of the tumor. Mostly in the best preserved parts the cells are cubic, roundish in shape, with an oblong, rather big, nucleus, more or less deeply stained (Fig. 7). The protoplasm of the cell is not well limited in contour and the cells seem to merge into other cells. In other parts the shape is more polygonal and flat, and where there are lumina or cavities surrounded by cells these are distinctly cubic or almost cylindrical, forming a complete layer all around, limiting

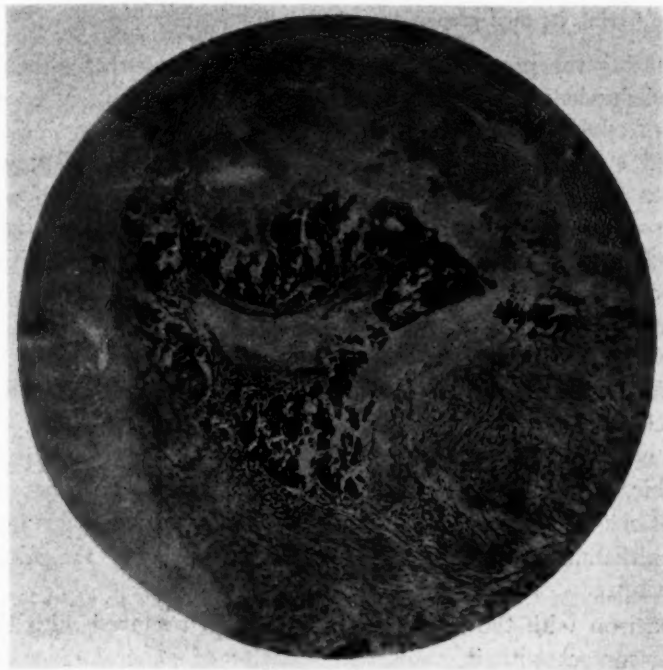


FIG. 9.—Extensive necrosis—a small vessel, and, around it, cellular masses are preserved.

the cavities very regularly, as is proper for glandular ducts or lumina and with nuclei generally toward the base of the cells.

In Fig. 5, near the adenomatous part, is a small mass of cells forming an almost oval and limited body. The cells in this are smaller. Degenerative and various changes of the cells are almost the rule.

Fig. 7 shows the protoplasm of most cells, as clear, divided in portions by thin threads; in many appear vacuoles which may take almost all the cell, pushing the flattened nucleus to the periphery. Hydropic degeneration, steatose, cellular inclusions, and gigantic cells of difficult interpretation appear also here and there (Fig. 8). Through destruction of cells, spaces are originated which are clearly distinguished from the adenomatous spaces, as the former have not a regular shape and the surrounding cells are also irregular in form and disposition.

Mitoses are not numerous and not regular.

Vessels are scanty and of only a capillary size; vascular spaces are more numerous, and the cells mostly in contact with it. This perivascular disposition is best visible in

the periphery of necrotic zones where everything is dead but for some few vessels and vascular spaces surrounded by cellular masses, giving the appearance of a perithelial disposition (Fig. 9). The cells here are smaller, rather round and their protoplasm not well limited, with round nuclei less deeply stained.

The stroma of the tumor deserves a brief description. We said that there is a capsule and thin septa starting from it and dividing the growth. This stroma can be called trabecular and it is the main frame. Besides there is the delicate network dividing the columnar strands; this is made of very fine fibrils penetrating even between small groups of cells, and having elongated, very thin nuclei. This can be called fibrillar.

But as shown in Fig. 5 there are large areas of tissue with fusiform cells, and in some sections such areas are surrounded by the fibrillar framework as if it were another kind of tissue having its own properties and growth.

Summarizing the previous descriptions we may say that attached to the stomach and duodenum was found a large solid tumor mostly encapsulated, composed of polymorphic, not well differentiated elements disposed in columns and strands, infiltrating the subserosa of the duodenum and the capsule, with scanty adenomatous portions, and alveoli of smaller cells and tubes, with a poor thin vascular arrangement; hence extensive massive necrosis and cellular degeneration, with a polymorphic connective stroma, resembling a parenchymal embryonic tissue partly differentiated, in a way to be compared to an unstriped muscular tissue.

Both parenchyma and stroma are, then, of embryonic character without a typical differentiation, but having a disposition which may allow us to speak of its probable origin.

The general lobular arrangement of the growth, its cells with tendency to grow cubic, though irregular and polymorphic, the appearance of adenomatous portions and of solid small tubes, speak for a typical growth of glandular epithelium, where the solid form prevails over the adenomatous proper.

A comparison with the thin layer of pancreas removed with the tumor and in close contact with it, shows a similarity of general disposition, and also few degenerative changes in its epithelium comparable to that of the tumor.

The seat of origin of the tumor could be supposed to be in the subserous coat of stomach or duodenum, or outside of these and penetrating later into them. Certainly the mucous and muscular coats and the pancreas could not be its origin. In any case it is necessary to think of an embryonic germ either in the stomach or duodenal walls or near them as the source of the growth.

The simplest supposition is that it is derived from an aberrant pancreas. We know their frequency and their possible location all along the gastro-intestinal tract and chiefly near the pylorus and the duodenum, according to Delhougne in the proportion of 58.3 per cent., and in the subserosa in the proportion of 15 per cent. They are miniature complete organs, well differentiated and generally without special structural particulars which dispose

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them to grow into a tumor. But besides these can be found incomplete formations, that is, ducts alone without glandular tissue, but with Langerhans' islands, islands alone (Lauche), or ducts and glandular tissue with masses of epithelial cells not completely differentiated, or with embryonal character.

That these aberrant pancreases may be the origin of tumors is admitted and for the adenomyoma of the stomach, especially, seems to be proved. But these are clinically unimportant, and the literature does not show cases of true neoplasm with progressive development whose origin can be traced in aberrant pancreas elements. Mathias, Beutler and Herxheimer do admit this as a possibility, but their cases are the least probable. These were extremely small tumors made of pancreatic germs with proliferation of adenomatous or myomatous character having then organoid structure, without any sign of progressive growth and certainly not to be considered true blastomata.

The cases of Askanazy, too, do not speak for the possibility of such origin as none of them is a true progressive tumor, and he himself says that the aberrant pancreas has not yet been found in relation with a true neoplasm. The same opinion has been expressed by Delhougne.

Such affirmations, though very important, cannot have an absolute value in refuting that possibility, and before doing so I think it is necessary to compare my case with cancers of pancreas proper. These are supposed to originate from the lining cells of the ducts, from the mucous glands of the ducts, from tubuli or gland tissue proper and from Langerhans' islands.

The duct-cell cancers are admitted to be cylindrocellular chiefly and of the adenomatous, cubic or polygonal, less differentiated, and the general structure of a solid tumor. Those derived from mucous glands of the ducts are characteristic of mucus production and the cells though irregular in size and shape have a tendency to be cylindrical (Helly-Rheiner). Such a schematic division can be accepted as an orientation.

Tumors in the pancreas, as elsewhere, do originate from elements which have the capability of regeneration, and to these cells is inborn the property of differentiation in various stages. Besides the same tumor cells, according as the tissue where they grow and the conditions of their development, may change considerably in shape and disposition. For these reasons we may find in the same pancreas cancer, solid and glandular formations, and cells of various shapes, even a tendency to polymorphism, with variations in the staining properties, and with various types of degenerations.

Comparing my case with true pancreas cancers, we find that in my case there is a general disposition of a solid lobular tumor with round, polygonal, cubic elements and with tendency to polymorphism. Rare are adenomatous formations, and very extensive the degenerations. This can be admitted as being close to a pancreatic solid tumor of glandular origin. But there are differences which are, chiefly, a more embryonic, undifferentiated character of the cells in general, their perivascular disposition in many parts and the

presence of large areas of connective tissue which is not a tissue reaction but, as I shall discuss later, a part of the tumor itself. For these reasons and for the theoretical ones above quoted, I believe that my case can be compared in some part to a glandular pancreas tissue cancer, in some others not, so that it is not proved beyond refutation that it can be of aberrant pancreas gland origin.

Can we think of it as coming from isolated aberrant Langerhans' islands? These are known to be present in the stomach and intestine very seldom without accompanying pancreatic tissue, but with ducts.

Following Lauche only four cases can be considered as positive, that is a case of Saltykow in which islands and ducts were found in the mesentery, a case of Delhougne, one of Askanazy in the stomach, and his own which he calls carcinoid of the small intestine. M. B. Schmidt also described a case in which many small carcinoids of the small intestine were found, with a combination of islands, pancreatic tissue and carcinoid areas. Saltykow derives the intestinal carcinoid from islands tissue, and calls them "tumores pancreatici intestini." In none of these cases were found characteristic qualities of a beginning true blastoma.

Here, too, before making a conclusion, it will be convenient to examine the neoformations known to arise from islands in the pancreas itself.

But before examining these cases I believe it is proper to review what is known about the so-called independence of the islands, and their capability of regeneration and proliferation. The absolute independence and delimitation of the islands from the surrounding glandular tissue is variously admitted. It seems to be possible, but usually there is a relation between the one and the other (Otani). There is the same difference of opinion about the possibility of the islands to transform into glandular tissue and the opposite. Laguesse, the chief exponent of this doctrine, and his pupils call it a "balancement," while Weichselbaum and many others deny it completely. They believe that in adult life neoformation of islands happens as in the foetal life, that is, from pancreatic ducts, and in course of time becomes exhausted. The regeneration can be from elements of the islands but especially from the ducts. The finding of islands tissue in connection with the glandular tissue is not a proof of a reciprocal transformation but it represents the final fixed developmental condition in which one can recognize the origin of islands from the glandular tissue and from the ducts. This view of Neubert is accepted also by Kraus.

The islands, then, constitute a highly differentiated tissue with determined functions and cannot be considered as a tissue in continuous germination.

According to Walz there are cells, which could be called *basal cells*, not only in the ducts but scattered between the glandular elements of the tissue and the islands. From these could be formed islands and glandular tissue, and eventually these cells could proliferate abnormally and remain in a stage of lower differentiation, forming a tumor which could be called "*basaliome*."

From these facts we are brought to admit as extremely difficult to accept

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the possibility of tumors arising from cells of the islands already differentiated. Tumors having origin from them have been described *adenomata* and *carcinomata*.

The first bears then the name of "*insular adenomata*" to separate them from the glandular tissue adenomata. Such a name should be applied only to veritable tumors, and not to proliferations of islands tissue which are a high grade of compensative hypertrophy (struma or adenoma insularis) in diseased pancreas, or perhaps developmental abnormalities in a normal pancreas.

Twenty cases are in the literature from the first case of Nicholls to the last of Warren. All were extremely small, well-isolated growths characterized by a resemblance of their elements to those of the islands. None had any sign of active proliferation or malignancy and clinically they have no importance. The one described by Walz as "basaliome" is to be compared to that of Rollet and according to Gruber is to be considered as a solid adenoma of insular formation.

These cases have been described as *malignant adenoma* originating from islands in the pancreas.

A case of Soprana's.—It was a cystadenoma proliferating as a cancer invading the organ extensively and with metastases and peritoneal implantations. The structure was chiefly of a tumor originating from glandular and duct elements, but there were well-limited formations similar to islands tissue and he thinks that this too contributed to the growth together with ducts and glandular cells. There are no proofs for such an opinion and probably these limited formations must be considered as a reactive proliferation.

A case of A. Vecchi's.—Man, aged sixty-three years, had had a big tumor in the left hypochondrium for nine months. At operation the large mass, which was retroperitoneal, was enucleated. Autopsy showed that it had developed laterally to the pancreas whose tail reached the bed of the tumor and was complete. Tumor of 18 by 20 centimetres; weight 2.5 kilograms; lobed, hard, encapsulated, at section rose-whitish with spongeliike portions containing mucous substance. Microscopically masses and strands of cylindrical, prismatic, high, conic cells, with definite contours disposed regularly along the fine vessels; rich nuclei, oval, rich in chromatin. Many degenerations of the cells, hence the spongeliike parts, and hyaline degenerations in the stroma. Posteriorly, inside the capsule, was found a small island of pancreatic tissue with islands and ducts. The growth was invading some of the islands intimately, mixing its elements with those of the islands in such a way as to make one think that their origin was in these. Other islands showed alterations to be interpreted as a proliferative reaction. He calls this growth an adenoma and thinks that it had arisen from the islands of a supernumerary caudal pancreas lobe of which a residual portion was still present. The reasons were the intimacy and affinity between islands and tumor cells, the similarity of these with islands cells, and their perivascular disposition.

I could not find in the figures given by Vecchi such cellular similarity; and the proof of cellular affinity and intimacy has no worth. The islands seem to be passive, infiltrated. The presence of a small pancreatic lobule almost intact is a proof against, as, if the growth had arisen in this, it would have completely destroyed it when attaining such a size.

Cancers of the pancreas originating from islands have been described by Fabozzi. In five cases he found in the zones between the tumor and the pancreas, an increase in number and size of islands, with hyperplasia and fusion forming large, cellular masses connected with the tumor and having the same staining and histological qualities.

Subsequent investigators have denied not only this origin of pancreas cancers in general, but also the possibility of a cancerous proliferation from the islands, and Fabozzi's theory seemed forgotten when later Horgan found cellular proliferations in cases of hypertrophy of the islands pointing to a possible malignancy, but without a real tumor, and two cases were published in America which deserve a special mention; the first published by Russell, Allan, Power and Robertson, the second by Thalhimer and Murphy.

These have in common a severe hypoglycæmia expressing itself in the first, a man of forty years with attacks of faintness and weakness occurring more frequently in course of time for eighteen months, and resulting in coma if food or sugar intake was delayed; and in the second, a woman of fifty-seven years, with attacks characterized by somnolence followed by great restlessness and irritability lasting one day followed by one day of almost continuous sleep. These attacks grew more frequent, until at last they were occurring every day with convulsions without loss of consciousness and followed by coma. The details of these cases and the complete investigations made in the first are extremely interesting, but not regarding our present question. The man was operated upon at the Mayo Clinic and a hard, nodular pancreas and tumors in the liver were found. A short time afterward he died and an infiltrating tumor of 5 centimetres was found in the tail of the pancreas with yellowish nodules and a small cyst and metastases in the liver. Microscopically the pancreatic tissue was seen to be replaced extensively by tumor cells embedded in a dense connective stroma and arranged in irregular strands and islands. The cells were of irregular size and shape, and staining reaction and arrangement, strikingly resembling cells of Langerhans' islands. The cytoplasm was well stained with slight basophile reaction, and the cell masses arranged about capillaries usually in two rows, occasionally in alveolar form, but with no evidence of glandular structure. Many degenerations were found in some parts, but no mitosis except in the liver tumors. Because of these characteristics and others, which anyone interested in the case will see better in the original paper, the authors conclude that the tumor is a carcinoma, arising primarily in the islands cells, and that there is evidence of hyperinsulinism from this tumor and especially from its liver metastases.

The second patient died in coma during one of the attacks. Nothing was found at the necropsy but about at the junction of the body of the pancreas with the tail a tumor nodule appeared, of 1.5 by 1 centimetre, slightly prominent, ovoid, firm, creamy white, well demarcated, incompletely encapsulated and seeming to invade the pancreatic tissue, but without metastases. Microscopically there was a parenchyma composed of cells which appeared to be identical with the cells of the islands, divided in masses and strands irregularly by dense connective tissue, and in some places there were small groups of tumor cells so isolated by connective tissue as to appear identical with normal islands, no typical mitoses. In other places were few cells larger than normal island cells of irregular shape, with hyperchromatic nuclei, atypical, and as if they were about to undergo proliferation. In some places and toward the edge of the tumor were aspects of malignancy characterized by slow growth and invasion. The author's conclusion is that the tumor was a carcinoma of a low grade of malignancy, originating in the islands cells and giving clinical manifestations of hyperinsulinism. This interpretation was accepted by Robertson, Wilder and Bensley.

The preceding review shows:

First.—That tumors arising from isolated aberrant Langerhans' islands have been an extreme rarity and none possessing the qualities of a progressive growth.

Second.—That malignant adenoma from island of an aberrant pancreas does not exist except for Vecchi's case which is not beyond refutation.

Third.—That it is possible, though extremely seldom, to find a true cancer in the pancreas with the characteristics of Langerhans' islands structure.

This last possibility has been proven now by two cases. But is it equally proven that these two tumors had their origin in the islands? If we think of the peculiar structure of the islands and of their characteristics, to be a well differentiated specifically functioning tissue with scanty proliferative regenerative power, it seems more justifiable to admit that tumors composed of cells of the Langerhans type are produced by proliferation of embryonic elements having the same properties as the ones which primarily originated the islands. Without thinking of an embryonal anlage separated from its parent and included in the pancreas we can admit that normally the cells which have the power of regenerating the islands are the formal cause of a tumor, for such elements are undifferentiated, have a high reproductive power and from them can come blastomatous formations which may repeat atypically either one of the pancreas components or some together. One ascribes this property to the cells described by Walz as above reported, or to those contained in the so-called indifference zone of Schapers and Cohen—that is to cellular proliferating centres having embryonic properties from which regeneration should come and later possibly tumors.

It would be far simpler to have a unitarian conception of the formal genesis of pancreatic tumors, and this conception could be formulated: The elements which have the function of regenerating the different tissues of the pancreas preserve in the adult life, some of their embryonic qualities and may, for unknown reasons, proliferate atypically and according to the various stages of differentiation these atypical cells reach, we see tumors of different composition. It is natural to see more frequently tumors of glandular and duct structure than tumors of islands structure, these being the highest in differentiation.

This conception does away with the useless or preconceived tentatives to assign to a definite tissue or elements of an organ the primitive source of a growth, which is almost always impossible. The fact that a growth repeats atypically some structure does not mean that its origin was in the ripe elements of the same.

Coming now from this digression to my case I find that the comparison of it with Langerhans' islands in diseased conditions and with the published tumors, can give some arguments in favor of a similarity.

These are: The distribution of the cellular masses sometimes in strands; the close connection of the cells as in the islands; the contact with the capillaries in many instances, without a separating *membrana propria*; the small

size of cells in many parts; the uncertain limitation of their protoplasm; the slight basophile staining (as far as could be ascertained). Besides, it is possible to find here and there a small areole (Fig. 5) rather well limited, with small cells resembling an island.

Against this origin from islands, or against the insular structure of the tumor, is the prevailing embryonic character of the cell masses, with no decisive differentiation, the few glandular formations and the quality of the special stroma, not dense, fibrous, as observed previously, but delicate, rich in cells, giving the impression of a tissue having a constituent part in the growth.

My conclusion is that such origin cannot be proved.

The third possibility is the origin from an embryonal germ included in the subserosa of the stomach or duodenum.

That such inclusions are really existing and perhaps more frequent than it is known, is shown by the publications of Askanazy illustrating various qualities of such inclusions, and trying to put them in relation with the cancer of stomach. In some of them pancreas lobules, stomach mucosa invaginations, ducts and cysts were mixed together, and in one also epithelial lobules without lumina resembling L. J. The connective stroma of such findings is also various and I think the fact is especially noteworthy that in some it was a soft tissue with abundant stellate formed cells or a delicate fibrillar tissue with flat nuclei.

Those formations are called blastoid by the author who discusses the possibility of cancer arising from them and later invading the mucous coat and ulcerating it so that in an advanced stage it is impossible to recognize its true origin. Whatever it may be for the cancer of stomach, it is important to remember the presence of such inclusions and the possibility of their transformation in blastomata.

As such formations are to be explained only by admitting the inclusions of entodermic germs it is evident that the future evolution may be in various directions: In one case the tendency may prevail to a complex of tissue, a blastoid or organoid formation, or to mucous membrane formation; in another to a pancreas tissue or to a less typical tissue nondifferentiated.

In my case, the conditions of the epithelial growth are these: Generally a solid mass, rarely of glandular type, with a type of cell more embryonic and difficult to compare with cells of a typical organ, but so disposed as to imitate a lobular structure; here and there perivascular disposition, and small areolæ of smaller cells. The stroma of the tumor can be so distinguished as there is: A capsule with its septa running through the tumor, having a fibrous and lamellar structure, and connective-tissue areas with triangular or starlike irregular cells in loose formation; moreover strands of fusiform cells regularly disposed in fascicles and such that a distinction between fusiform connective cells and small unstriped muscular fibres is difficult. These connective formations cannot be interpreted as a reaction of tissue to the invading tumor, first, because of their cellular structure and then of their

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disposition in masses and bundles; secondly, because the tumor has no development into other tissue or organs from which a connective proliferation could arise. They are then a constituent part of the tumor.

These considerations bring me to conclude that this tumor is a peculiar one, solid, with scanty adenomatous formation, with a peculiar connective tissue, with cellular types and disposition to be compared to pancreatic atypical glandular structure, to islands atypical structure, but not so well definite to assign to one or to the other, or to both together, being generally too much atypical and undifferentiated. Forcibly we are induced to think of a more primitive and undifferentiated germ as its formal cause, that is an entodermal one which in its later blastomatous development took the direction of an atypical pancreas structure but so atypical that none of the types has been reproduced in a characteristic way.

Location of the Tumor.—Two possibilities I have considered already. *First*—The origin from embryonic elements in the subserosa. *Second*—From such ones in the gastrocolic ligament.

The first seems the more probable. Like many exogastric connective-tissue tumors, this grew where it was easier, that is, downwards, occupying in part and displacing the gastrocolic ligament, and infiltrating only later the longitudinal coat of the duodenum. If it had been born inside the ligament, this would have covered its anterior surface completely, which, instead, was free from it.

Embryonal formations included in this part of the omentum are unknown to me. For analogy with Saltykow's case, of pancreas germ in the mesentery, made of ducts and islands, and with the possible presence of entodermic elements in lymph-nodes (as in a lymph-node of pancreas pancreatic tissue was found by Nakamura) the presence of embryonal germs could be supposed possible.

Clinical Considerations.—The diagnosis of rare cases is generally not and cannot be made correct, and diagnostic refinements suggested in some instances after operations or necropsies, are mostly a consequence of theoretical or so-called logical considerations very seldom adaptable to practice. I shall not venture to say that cases like mine will be correctly diagnosed in the future, but their possibility will be considered.

Direct diagnoses of a perigastric duodenal tumor could be deduced by such signs: The presence of a movable tumor which could be demonstrated to have a relation with the stomach and duodenum without alterations of their walls as proper of carcinoma. This can be reached partly by air insufflation, and better by accurate X-ray investigation. In my case the rays showed the stomach pushed to the left and the greater curvature having the shape of a sac and situated much below the umbilical line, while the tumor shadow was continuous with the pyloric portion. The stomach had a notable delay in emptying. That seems to me enough to make a diagnosis of tumor in relation with the stomach.

A differential diagnosis should consider the seat of origin of the tumor and its nature. The possibilities are these:

Carcinoma of Stomach.—This may, in two instances, appear as a large tumor extrinsic to the organ. The first is, when having origin from the mucous coat it grows outside the walls, forming a large mass apparently attached only to the organ. I know only a case of Konjetzny and one of Knoflach and Eichelter from Eiselsberg's Clinic, which was developed toward the diaphragm. I myself have seen one such case, and another which was thought to be similar proved later to be probably a malignant carcinoid of extragastric origin.

The second instance is when a small stomach growth gives origin to large glandular metastases which impose for an extrinsic gastric tumor, as perhaps everybody has seen from time to time, in the lymph-nodes of the small curvature, but very rarely in those subpyloric or subfundal, or in the omentum forming in this a large mass. In a case of Konjetzny there was in the pyloric region a tumor of about 5 mk. size, and the metastasis in the omentum was larger than a foetal head.

Carcinoma of Transverse Colon with extracolic development, that is, in the gastrocolic ligament, or with metastases in the lymph-nodes.

This was seen by me in one case, and recently V. Ascoli has published such a case diagnosed by him and operated by R. Alessandri successfully.

According to my experience, extrinsic development of colon cancers is rather more frequent than in those of the stomach and not always accompanied by typical symptoms.

Sarcomata and Other Benign Tumors of the Stomach and rare cases, like dermoids (see two cases reported by Eusterman and Senty from Mayo's Clinic) may develop outside when they have a large base in the organ walls, growing in different directions. The most common is downward as they originate chiefly in the anterior or posterior wall near the greater curvature, and their development can proceed between the layers of the gastrocolic ligament. (Pseudonetz tumors of Borrmann.)

Subjective signs, like pain and impaired function, may bring one to locate the growth correctly, but such symptoms either were missing, or vague and not typical, and in such cases various diagnoses have been made as one can see in reviewing the literature of stomach sarcomata. We may expect that insufflation of the stomach and especially an X-ray investigation will throw more light.

Reviewing the experience made in cases of sarcomata and extrinsic growths of this organ we find that in none of those submitted to X-rays was the diagnosis made. A negative X-ray finding will not be sufficient to preclude the origin of a tumor from the stomach. I believe that such negative cases will be rarer and rarer in the future if doubtful cases will be examined repeatedly, and if peculiar deformation and displacement of its position will be

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found, the diagnosis can be directed toward the suspicion of extrinsic gastric tumor. Pneumoperitonæum and gastric insufflation may be practiced and aid toward a correct diagnosis (C. Desseker).

Tumors of the Omentum.—When solid and non-infiltrating, a condition which is very rare, these tumors may draw the stomach downwards and give origin to mistakes in diagnosis. I have not found decisive symptoms for a differential diagnosis. But the X-ray examination can certainly distinguish the relation of tumor and stomach.

The possibility of tumors developing in the upper part of the abdomen are many; and it is not the scope of this paper to consider all or to analyze the possible errors with tumors of other organs. These have been described by Alessandri, Lofaro, Konjetzny, Amelung and others, and I refer the reader to their papers.

In conclusion, there are some rare epithelial tumors arising from the walls of stomach or duodenum, which deserve a special pathological and clinical consideration. These tumors, together with connective-tissue tumors of stomach, especially sarcomata, and with stomach and colon cancers growing exogastric, constitute a class of abdominal tumors which in the future must be included in the diagnostic possibilities, and sometimes may be diagnosed correctly if the clinical and anatomical facts will be kept in mind.

In cases like my own the name of perienteric carcinomata would be more correct perhaps; a name which, being more general, eliminates suppositions about origin, which cannot be proven adequately.

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THE PREVENTION OF CARCINOMA OF THE GALL-BLADDER

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IN RECENT years, much attention has been directed towards the prevention of cancer by the education of the public concerning those various lesions which are generally considered to be precancerous. These efforts have, however, been concerned chiefly with cancer of the lip and mouth, the stomach, the breast, the rectum and the female genital organs. It is an astonishing fact that little or no emphasis has been placed upon the possibility of the prevention of cancer of the gall-bladder. In a paper presented by Doctor Ewing¹ himself, at the International Symposium on Cancer at Lake Mohonk, New York, in 1926, on "The Prevention of Cancer," nothing whatever was said about the possibility of the prevention of cancer of the gall-bladder. Moreover, I have not been able to find any article that has been published, at least in recent years, dealing particularly with the prevention, although, in occasional writings, attention has been directed to the frequency of carcinoma in this region.

It is difficult to understand why cancer of the gall-bladder has been neglected in all of the educational work that has been done by the American Society for the Control of Cancer and other similar organizations. It would seem that there could be only two reasons for this neglect: first, that it is considered to be a rare disease, and, second, that there would seem to be no way of preventing it. It is the purpose of the present paper to attempt to show that both of these ideas are erroneous.

The great frequency of carcinoma of the gall-bladder as compared with

Name of authors	Buday		Bejach		Redlich		Feilchenfeld		Riechelmann		von Berency and von Wolff	
The number of autopsies from which the statistics have been compiled	5,530		6,808		5,002		5,022			19,908	
Number of cases of cancer	336		692		496		507			2,314	
The organ	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.
Esophagus.....	6.21	20.3	0.8	17.3	2.8	21.3	1.6	20.0	1.4	11.88	0.61
Stomach.....	38.42	16.36	36.5	31.3	39.9	39.6	39.9	25.2	46.6	34.1	48.90	20.45
Intestine.....	5.64	1.05	8.2	6.1	4.2	6.1	4.3	4.3	3.7	3.9	5.34	2.75
Gall-bladder.....	1.12	2.10	1.9	8.5	3.5	10.8	1.2	9.1	3.9	9.5	2.77	10.18
Breast.....	0.56	5.80	12.5	0.35	12.2	12.6	0.3	8.3	0.09	6.85
Ovary.....	14.78	2.1	5.1	4.7	4.0	8.16
Uterus and vagina.....	45.40	13.3	14.1	17.7	24.6	35.99
Uterus.....	44.35	34.85
Vagina.....	1.05	1.14

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carcinoma of other organs is shown in the table compiled by von Berencsy and von Wolff:²

It will be seen from an examination of this table that carcinoma of the gall-bladder has a very marked tendency to occur more often in women than in men and that it constitutes in most of the statistics between 8 and 10 per cent. of all carcinomas in women. It would seem fair, therefore, to conclude from the various statistics which have been already presented that carcinoma



FIG. 1.—A typical example of carcinoma of the gall-bladder associated with calculi.

of the gall-bladder is a comparatively frequent disease and because of that reason deserves our attention.

In this country, also, the frequency of carcinoma of the gall-bladder seems to be about as great as in the table given above. The mortality statistics³ of the Bureau of the Census for 1926 state that in the registration area of continental United States there were, in 1925, 9,558 deaths from cancer of the liver and gall-bladder. In 1926, there were 9,635 deaths. It is true, of course, that all of these deaths were not due to primary carcinoma

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of the gall-bladder, but since other carcinomas which cause metastases to the liver are listed separately under the œsophagus, stomach, intestine and rectum, the presumption is strong that most of these cases listed as carcinoma of the liver and gall-bladder were either primary carcinomas of the gall-bladder or primary carcinomas of the liver. The latter tumor is known to be rare. It would seem fair, therefore, to conclude that the majority of cases listed as carcinoma of the liver and gall-bladder were primary carcinomas of the gall-bladder. Primary carcinoma of the other portions of the bile tract is known to be rare as compared with carcinoma of the gall-bladder. During the same two years, the total deaths from cancer of all kinds were as follows: in 1925, 95,504 deaths, and, in 1926, 99,833 deaths. This would indicate that carcinoma of the gall-bladder constitutes roughly between 8 and 10 per cent. of all carcinomas and that its incidence for the general population is about 9 per 100,000. This is a very considerable number of deaths from this cause. As listed in the mortality statistics, deaths from cancer of the gall-bladder are about three times as frequent as from that of the lip, about one and one-half times as frequent as all cancers of the lip and buccal cavity, about twice as frequent as cancer of the rectum, of about the same frequency as cancer of the breast, about two-thirds as frequent as cancer of the female genital organs, and a little less than one-half as frequent as carcinoma of the stomach. It should not necessarily be inferred from these figures, however, that the occurrence of carcinoma of the gall-bladder in comparison with other organs is actually so high as it would seem to be, because nowadays many people with cancer of the other parts of the body mentioned are cured by surgical and other methods and, therefore, many cases of those cancers would not appear in the mortality statistics. The figures which are given merely show the deaths from the various types of cancer.

Concerning methods of prevention, the most outstanding fact is that carcinoma of the gall-bladder, in the great majority of cases, is associated with gall-stones. The frequency of the relationship between carcinoma of the gall-bladder and gall-stones is so great that various statistical studies have shown that in from 69 (Musser⁴) to 100 per cent. (Janowski⁵) of cases of carcinoma of the gall-bladder, biliary calculi are present. Lentze,⁶ who has recently studied the statistical incidence of gall-stones in cases of carcinoma of the gall-bladder from an extensive review of the literature, considers that cholelithiasis is practically always the primary condition. In this opinion he is not alone. Almost all of those who have studied this question believe that the evidence is overwhelming that when calculi are present they have preceded the development of the carcinoma. They should, therefore, be considered as being a definitely precancerous lesion. It seems unnecessary to present here in a detailed manner all the evidence in favor of this view. It is, perhaps, sufficient to call attention to a few facts. The opinion which has been expressed by some writers that the calculi are the result of the carcinoma seems to be supported by no evidence. For example, Siegert⁷ showed that, although calculi were present in ninety-four cases of a total of

ninety-nine primary carcinomas of the gall-bladder which he collected, they were present in only two of thirteen cases of metastatic involvement of the gall-bladder. Rolleston and McNee⁸ collected twenty-five other cases of metastatic involvement of the gall-bladder and found calculi present in only one. Therefore, in the total of thirty-eight cases of metastatic carcinoma of the gall-bladder, gall-stones were present in only three cases, an incidence of 8 per cent., which is well within the normal limits of incidence of gall-stones. What would seem to be conclusive evidence of the importance of the factor of cholelithiasis in the production of carcinoma of the gall-bladder seems to have been supplied by the experiments of Leitch,⁹ of the London Cancer Hospital Research Institute, who found that when he introduced human gall-stones and even ordinary pebbles into the gall-bladders of guinea-pigs there resulted a remarkable change in the epithelium of many of the cases, which he considered to be entirely characteristic of carcinoma. Although metastases of distant organs did not occur, nevertheless, there was marked invasive growth of the carcinoma into the liver, the omentum and even into the chest wall. The illustrations accompanying Leitch's article are very convincing. It would seem, therefore, that there can be no reasonable doubt that the presence of calculi in the gall-bladder predisposes the individual to a carcinoma of that organ. This would seem to be particularly the case if the patient is a woman beyond the age of forty. It is unnecessary in this article to discuss how the gall-stones may operate to produce the carcinoma.

Another important consideration is the question: In what proportion of cases of cholelithiasis does carcinoma of the gall-bladder occur? The various statistics which have been published on this point vary greatly. Lentze⁶ found, in a collective study, that in 557 cases of cholelithiasis in women over thirty-nine years of age, there was an associated cancer of the gall-bladder in 5.1 per cent. Rolleston* states that 4.5 per cent. of all cases of cholelithiasis are accompanied by carcinoma of the gall-bladder. Moynihan* gives 5 per cent., Riedel* 7 to 8 per cent., Mayo-Robson* 10 per cent., Schröder 14 per cent. In our own cases at the Barnes Hospital 8.5 per cent. of all cases of stones in the gall-bladder have been associated with carcinoma of that organ. According to Leitch, the lowest incidence reported is that of Candler, who found in post-mortem statistics from an insane asylum an incidence of only two cases of carcinoma in 315 cases of calculi. The highest incidence, according to Leitch, is that reported by Slade, who found 30 per cent. It is, of course, probable that the incidence reported by surgeons, and coming from the general hospitals, is somewhat higher than that of the general population, because practically all of the cases of carcinoma of the gall-bladder sooner or later reach the hospitals, but many of the cases of ordinary cholelithiasis without carcinoma do not. It would seem reasonable to conclude, however, that at least 4 or 5 per cent. of women in the cancer age, who have gall-stones, will develop carcinoma of the gall-bladder and

* Quoted from Leitch.

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perhaps further study will show that the incidence may actually be much higher.

If we accept the idea that gall-stones represent a definite precancerous lesion of the gall-bladder, the most obvious consideration in the prevention of this condition is the question of the possibility of diagnosing biliary calculi. The improvement in diagnosis of lesions of the biliary tract, which has been made possible by cholecystography, now enables us to diagnose biliary calculi with practically 100 per cent. of accuracy. It is true that the stones themselves cannot always be visualized, but in our experience at the Barnes Hospital every case of biliary calculi, without exception, which has come to operation, has revealed itself on cholecystographic examination, either by actual visualization of the calculi or by the demonstration of an unquestionably pathological gall-bladder. It would seem, therefore, that no particular difficulty should be encountered in the recognition of this very definite precancerous lesion.

A most important consideration is, of course, the question as to whether or not we should advise the operative removal of a calculous gall-bladder, or at least of its contained stones, from the point of view of cancer prevention entirely apart from the other more usual operative indications. This question naturally involves the consideration of the risk of cancer on the one hand as compared with the risk of operation on the other. The operative mortality in uncomplicated cases of cholelithiasis before there has been much damage to the liver, to the heart, to the kidneys, etc., should not be more than 1 per cent. This is, approximately, one-fourth or one-fifth of the danger of death from carcinoma. At the hands of experienced surgeons, the operative mortality, even including all of the bad risks which present themselves as examples of long-neglected biliary-tract disease with many incurable complications, is still about only 3 per cent. or less. Our own mortality at the Barnes Hospital during the last three years has been 1.5 per cent. This series has included patients of all ages and with practically all of the known complications of biliary-tract disease. Deaths from all causes which have occurred in the hospital have been included in the operative mortality. It is significant, however, that most of the deaths have been due to incurable complications of neglected disease of the biliary tract. Younger patients, in better physical condition and with fewer complications, would almost certainly present a much lower operative mortality. From the standpoint of cancer prevention, it would seem to be our duty to inform patients with gall-stones that, in general, they have a greater chance of dying from carcinoma of the gall-bladder than they would have by a properly performed operation. This phase of the question is in addition to any other features of the case which should be regarded as ordinary indications for operation. The danger of cancer is especially great in women past forty, and this danger is probably increased if they come from cancer families with an inherited predisposition to its development.

EVARTS A. GRAHAM

SUMMARY

Since gall-stones seem to have an etiological relationship to the development of carcinoma of the gall-bladder in nearly all cases, the occurrence of most if not all cases of carcinoma of the gall-bladder could be prevented by cholecystectomy in cases which present evidence of gall-stones, regardless of the presence of those symptoms which would ordinarily compel a patient to have an operation. The diagnosis of gall-stones is now easily and accurately made by cholecystography. In uncomplicated cases of gall-stones there is less risk of death from the operation of cholecystectomy than from the development of a carcinoma of the gall-bladder, particularly if the patient is a woman of middle age. Contrary to the general opinion carcinoma of the gall-bladder is not a rare disease, but a very common one. It constitutes approximately 8 or 10 per cent. of all carcinomas.

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ELECTROSURGERY IN GYNÆCOLOGY

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MEN who fill our professional ranks, whether in medicine, religion, or law, are habitually conservative. This salutary mental attitude expresses itself peculiarly in our communal relations; namely, when a new idea appears which is more or less subversive to old notions and practices, he who originates the idea must strike sledge-hammer blows in order to secure even a momentary attention. This must then be followed by a long, patient propaganda of proclamation and advertising until in the grand finale the public, indifferent at first, is aroused, proceeds to discuss, and finally accepts the iconoclastic proposal as a long-accepted fact of its own invention and asks wonderingly, "Why such a pother? What after all is there new about the thing? We knew it all long ago!"

Such is the history of the therapeutics of radium about which the public is just opening and rubbing its eyes after a quarter of a century of sleep. And so, too, has it gone with the electrosurgery marvelously wrought out by William Clark, of Philadelphia, in 1908-1910, and promulgated with all the documentary evidences and data necessary to establish its rights of eminent domain over a new and large arena in the surgical realm.

In this latter field, however, we are still in the proclamation stage when success waits upon iteration and reiteration—both beneficent procedures, for which no apology is necessary—while we continue to hammer at the general surgeons' doors and shout aloud our incontestable attainments, as we beg for a meed of generous recognition in all our large hospitals.

Here we supplant our ancient procedures in the operating amphitheatre with electric current oscillations of a million or more a second and regulable from a minute needle-point spark up to a flashing, withering, sword-like flame, made superficial or penetrating at will. With George A. Wyeth's knife (acusector) we cut tissues as a hot knife goes through butter, or we dry the structures to a powder, or, again, we boil or coagulate without carbonizing, the current exerting its potency at or close around a needle point or a small ball, the active agent held in the operator's hand remaining a cold field.

Unlike radium, which is a ray therapy, electrosurgery is thoroughly surgical and at once a vigorous, insistent competitor with those age-long badges of our profession—scalpel, ligature, needle and suture, supplanting these time-honored instruments in their own arena and in appropriate cases relegating them to the *Rumpelkammer* as mediæval, crude, antiquated. Although the field of this new electrosurgery is a broad one, its preferential work lies conspicuously in the destruction of cancer where in numerous instances it reaches

a perfection of *ne plus ultra*. I adhere as my theme in this brief memorandum to one of its more limited fields where it does not appear altogether at its best advantage. I speak of cancer in the female generative tract. One who wishes to judge it for the first time should observe a skilled operator in the surgery of the mouth or of the brain.

In gynecology, electrosurgery is preferable in:

1.—Cancer of the external genitals: vulva, clitoris, Bartholin's glands and the external urethral orifice.

2.—The destruction of metastatic or suspected inguinal glands.

3.—Cancer of the vagina in its primary form and the destruction of metastatic nodules in the vaginal wall.

4.—Cancer of the cervix, cooking and destroying the tissues until the cervix can be reamed out in a hollow cone for the better lodgment of an effective radium treatment.

5.—Lower abdominal surgery, cooking superficial cancerous nodules remaining after the enucleation of the large parent mass, whether uterus or ovaries.

6.—A scirrhus nodule in the wall of the intestine, which can be necrotized even through the entire thickness of the wall and then left *in situ* after drawing the peritoneum over the area with fine silk sutures.

7.—Papillomatous tufts on the peritoneum, which can be withered down to the base and out of existence by an exposure of a fraction of a second duration, requiring no ligatures or sutures. In this way many can be wiped out in a minute, a precious saving of time.

8.—Areas of carcinoma left on or in the pelvic wall after an extirpation.

9.—Enlarged glands on the pelvic floor, which are punctured and coagulated thoroughly and left *in situ*, as well as any gland at a bifurcation of a large vessel, saving a prolonged, difficult operation at a critical period after a panhysterectomy.

10.—Papilloma of the bladder, forming a brilliant and speedy way of attack either by cooking its pedicle if it is pendulous, or by coagulating the flat, raspberry masses, stopping hæmorrhage and extirpating the tumor or reducing the mass for radiation.

The value of electrosurgery in all these situations lies in the perfect control of the current which can be applied as effectively at any reachable distant point by a stiff wire as on the surface of the body; that is to say, at the vaginal vault, deep in the pelvis, in the bladder through the aëroscope, up in the rectum at the pelvic brim in the knee-chest posture, or down in the larynx or in the fauces, and even in the trachea and bronchi.

The advantage over scalpel and suture is perhaps more apparent in that the tissue cooked and sterilized *in situ* is often not removed but advantageously left to be thrown off spontaneously in a few days. In treating large glands, it may be well at times to puncture and coagulate thoroughly and then to incise and curette away all the friable tissues, to be followed by a thorough cauterization of the capsule from within. A metastatic gland

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lodged in the bifurcation of a large vessel is admirably managed in this way by an experienced operator.

The value of electrosurgery in vulvar cancer is at once apparent in carcinoma of the entire vulva, always an awkward knife, forceps, and ligature operation. Here the cutting current reduces the bleeding of the incision to a negligible minimum. Then follows a careful dissection, undermining while raising the mass. Any larger vessel seen as it is approached through the fat is caught with delicate forceps slightly curved at the tip and divided; finally, the few vessels so controlled are sealed by touching each forceps with the coagulating current when they wither and are sealed (Grant Ward). So *pari passu* the new operation advances to its finale in far less time than with a scalpel dissection. Great care should be taken not to contaminate the wound during such a knife-and-fork operation. The flashing current can be used advantageously to sterilize any ulcerated areas on the surface.

It must not be reckoned a small matter here that there is a great saving of ligatures as well as of time in operating, not to pass unnoted the few and simple instruments sterilized. Nor, again, should we overlook the fact that the post-operative discomforts are greatly lessened, while these cases are either ambulant at once or in a very short time, substantially increasing the turnover of the hospital. There is also, I think, a wise inclination on the part of experienced electrosurgeons to leave many of these sterile wounds open and to treat them with a 2 to 3 per cent. mercurochrome solution daily, protecting them under simple dressings from exposure and contamination. Granulations spring up with surprising rapidity, and a soft flexible scar is the outcome—a matter of extreme importance in many familiar situations, mentioning the periphery of the eye as an example. The field of local anæsthesias is extended to the satisfaction of many patients.

While we sing the praise of this new electrosurgical field, he will do best by his patient who also thoroughly knows our older methods and above all is cognizant with the phenomenal results of radiotherapy, including X-ray though less potent and dependable.

As a rule, most of our carcinoma cases need efficient radiation either to inaugurate or to complete the cure, whatever other adjuvant methods we may adopt. Electrosurgery is often a preliminary to facilitate radiation, serving an excellent purpose in removing and sterilizing a massive disease down to its base to insure a more direct, efficient application of the succeeding therapy. On the other hand it is sometimes well to apply radium first, for its effects act in the more distant peripheral zone, to be followed in a few days by the more localized radical electrosurgery. It is indeed a happy concomitance that both of these agencies are not mutually exclusive but coöperative as they work together to promote the desired result. By and large, be it said, it is rare that a new method coming in wholly displaces the old, but rather does it supplement and increase its effectiveness and enlarge its territory.

CARCINOMA OF THE PROSTATE*

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FROM THE UROLOGICAL SERVICE OF THE MEMORIAL HOSPITAL

CARCINOMA of the prostate still holds its place as the most baffling of urological conditions. We know little of its etiology. In but a small percentage of cases is the diagnosis made sufficiently early to give any sort of treatment a fair chance of success. Even if an early diagnosis be made there is no general agreement as to the best way to treat this neoplasm. We hold that the possibilities of radical surgery have been thoroughly exploited while the effective use of radiation is still far from the practical limits of its application to this disease. This paper is written in an attempt to analyze the reasons for the failures of the past, to discuss our present ideas on the subject and to suggest further improvement in the control of the disease by radiation.

Diversity of Therapeutic Policies.—Young, who has employed the quite intricate radical operation for cancer of the prostate reports twenty-seven cases, the first in 1904 and the last in 1927,¹ just a little over one a year. This would seem to indicate how very few cases coming to his service are believed to be suitable for radical operation. In a large majority of these cases the diagnosis of carcinoma was made before operation. In a fair percentage the carcinoma had extended beyond the limits of the prostate. In our own experience at the Memorial Hospital less than 5 per cent. of all prostatic cancers were confined to the organ. In Young's series, eight patients of the twenty-seven are reported alive and well for periods varying from three to thirteen years after operation. Young believes that the radical operation should be performed in selected cases. In other cases he does a modified radical operation using radium at the time of or after operation. In certain cases he has used radium alone or in combination with X-ray therapy.

Raymond Dossot² after an extensive study of prostatic carcinoma, in 1926, concluded that radiation was better treatment than surgery as being more benign in its application, but stated that the possibilities of radiation had not been fully investigated. At that time he regarded all treatment as palliative only. In a more recent article on the subject³ he reiterates his pessimism as to any form of therapy except palliation, attacks Young's radical prostatectomy vigorously and sees the best results in cystotomy and palliative radiation.

Young⁴ in replying to Dossot's attack on radical surgery states that since the adoption of his recent technic thirty-five radical prostatectomies have been performed for carcinoma of the prostate with but one operative death.

Smith formerly put much faith in Young's operation but more recently⁵ seems to have become impressed by the possibilities of deep X-ray therapy for growth restraint. He noted the marked histological changes occurring in a carcinomatous prostate so treated.

Marion and Wildbolz⁶ believe that operative removal offers the only chance of control. Wildbolz found forty of 145 patients with prostatic carcinoma suitable for this form of therapy and so treated them.

Bumpus reviewed the cases at the Mayo Clinic in which operation had been undertaken for benign hypertrophy but in which carcinoma had been discovered on routine

* In part from the Guggenheim Fund for Urology.

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microscopic examination of the sectioned organ. He believes that the best chance for cure by surgery lies in this group of cases, namely those in which the neoplasm is not clinically demonstrable but proves to have carcinoma on histological section. In a clinical study of 1,000 cases Bumpus⁷ states that in many cases the malignant disease was discovered only at operation but when it was also clinically evident the results were poor. He further states that in his opinion the most satisfactory form of treatment is operation followed by radiation.

Chute⁸ deals simply with the urinary retention caused by the neoplastic process. He does a partial prostatectomy, repeating it if obstruction recurs with gratifying palliative results. Most urologists believe that partial prostatectomy under these circumstances results in only very temporary control of the urinary retention and prefer the catheter or permanent suprapubic drainage.

Causes of Failure of Treatment.—The natural history of prostatic carcinoma presents many obstacles to effective therapy. The protean forms of the neoplastic process, lack of definitive symptomatology, the simulation of benign disease, make early and accurate differential diagnosis difficult. Radical surgery and palliative operations are quite generally conceived and executed with total disregard of the true biologic nature of the problem that must be met. Radiation has also failed to produce the best results, but in its conception it is sound. Effective application of radiation to prostatic carcinoma can only keep pace with the fundamental progress of the science of radiology. To date this form of therapy has been largely empirical in its application to new growths in the prostate. Only of recent years has it become apparent that more accurate methods and nicer adjustment of dosage to the biophysical reactions of normal and neoplastic tissues are productive of superior results. We have already felt the force of these advances and find that their application to the problem in hand has resulted in gradual improvement in the response of these malignant tumors to radiation.

The early local extensions of the disease have been noted with appalling frequency by most observers, yet few seem to appreciate the still greater and earlier incidence of pelvic lymphadenopathy. In Dossot's series² metastasis to the regional nodes in the pelvis occurred in 89.4 per cent., while Pasteau, quoted by Dossot, described this event in sixty of seventy-one observations.

A point of still greater importance bearing on the choice of therapy is the early infiltration of the capsule of the organ by the neoplastic process. Before local extension can be appreciated the new growth has frequently invaded the fibromuscular capsule by way of the loose cellular septa, gaining ready access to the small venules of the surrounding prostatic plexus. These veins are rapidly invaded by tumor cells rendering surgical intervention an impossibility without immediate dislodgment of tumor emboli, followed by distant metastasis. While we are not yet armed with the figures we believe that this type of extension occurs as early and with almost as great frequency as does extension by way of the lymphatics and the regional nodes. Certainly both events precede the direct gross anatomical extensions of the disease. The involvement of the capsule in the manner described is often noted by the surgeon when he fails to find a satisfactory "line of cleavage" between gland

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and capsule. It also explains the prompt and frequent post-operative recurrences, as few operators are so radical as to remove the last shred of infiltrated capsular tissue along with the entire venous plexus. Nor is this all. We have further evidence of a convincing nature that adenocarcinoma is frequently primary in the accessory prostatic glands at the bladder base, variously termed the subcervical group, glands of Albarran, *etc.*, these tumors later extending into the substance of the prostate proper, fungating through the bladder mucosa, or both. Furthermore, the earliest direct extension of the disease when primary in the true prostate is frequently in the direction of this group of accessory glands. In our material, primary or secondary involvement of this group is more frequent than the time-honored extension to the seminal vesicles.

Pelvic lymphadenopathy occurring in a very high percentage of all cases of carcinoma of the prostate, a high early incidence of capsular infiltration and venous thrombosis by tumor cells, frequent primary or secondary involvement of the accessory glands at the bladder base, all often present when the patient is first compelled to seek advice, constitute an insurmountable barrier to the successful surgical treatment of the disease no matter how radical its conception and execution.

Age Incidence.—The age incidence of cancer of the prostate does not differ greatly from that of benign hypertrophy so that this factor alone is of little value in differential diagnosis. Young in a series of 898 cases of benign hypertrophy showed that 794 or 88.4 per cent. occurred between the ages of fifty and seventy-five. In our present series of 280 cases of cancer of the prostate at the Memorial Hospital 197 or 86.6 per cent. fall in the same age group.

TABLE I
Age Incidence on Admission of Carcinoma of the Prostate in 227 of 280 Cases Studied at the Memorial Hospital

	Number of cases	Percentage of group
Under 34.....	1	0.4
35 to 39.....	3	1.3
40 to 44.....	3	1.3
45 to 49.....	6	2.6
50 to 54.....	26	11.4
55 to 59.....	42	18.5
60 to 64.....	44	19.3
65 to 69.....	50	22.0
70 to 74.....	35	15.4
75 to 79.....	13	5.7
80 to 84.....	3	1.3
85 to 89.....	1	0.4
Total ages 50 to 75.....	197	86.6
Total entire group.....	280	99.6

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The peak age group for benign hypertrophy occurs, according to Young, at fifty-five to fifty-nine. The peak age group for cancer in our series is at ages sixty-five to sixty-nine, ten years later. However, this is of academic interest only for the difference for each five-year period is relatively slight. We present a table of age incidence comparing groups reported by various authors with our own experience.

TABLE II
Age Incidence of Carcinoma of the Prostate

Ages	Young, 1909 111 cases Per cent.	Bumpus, 1921 361 cases Per cent.	Deming, 1922 100 cases Per cent.	Barringer, 1930 280 cases Per cent.
40 to 50.....	1.8	2.7	3.0	3.9
50 to 60.....	22.5	21.6	17.0	29.9
60 to 70.....	45.5	51.2	45.0	41.3
70 to 80.....	27.0	22.1	25.0	21.1
80 to 90.....	3.6	1.2	10.0	1.7

The statistics show no marked disagreement but our experience shows a slight increase in the earlier age groups with a corresponding decrease in the later years. However, these are all relatively small series and a truer picture would probably be given by averaging all the figures.

Symptomatology.—The symptoms of cancer of the prostate are not easily differentiated from those of benign hypertrophy, for both conditions are often present at the same time. A prostatic carcinoma is frequently superimposed upon a benign hypertrophy but many cancers develop in non-hypertrophied prostates as well. An earlier diagnosis usually is made where the neoplastic process develops subsequent to the benign hypertrophy. It is not surprising that even competent urologists often fail to recognize these superimposed cancers as the true condition is often masked by oedema. Hard carcinomatous nodules are easy to miss when covered by oedematous prostatic tissue. We have found that after subjecting these doubtful or suspicious superimposed cases to a cycle of high voltage X-ray, causing the oedema of the hypertrophied organ to disappear, the diagnosis is easier. Then the hard cancer tissue stands out sharply defined from the elastic enlargement of the benign hypertrophy.

The initial symptoms of carcinoma of the prostate fall into two main groups; 1, urinary symptoms; and 2, pain. The urinary symptoms are usually the first observed by the patient and therefore the most important from the point of view of early diagnosis. The two most common symptoms occurring early in the disease are frequency and difficulty of urination. In 82 per cent. of our 280 cases these two symptoms were the first exhibited. Other common symptoms associated with the above are nocturia, retention, hæmaturia, urgency and incontinence.

The symptoms of pain which cause the patient to consult his physician are, in the order of their importance; painful urination, backache, pain down the thighs and legs ("sciatica"), pain in the lower abdomen and pelvis, pain in

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the hips, groin, penis, rectum, and perinæum. Most of these are late symptoms, due to direct invasion of the bladder neck, to pressure on nerve trunks by invaded pelvic nodes, obstruction to the venous circulation from the same cause, or to distant metastases, especially to the bones. We here present a tabulation of the initial symptoms occurring in 280 cases of cancer of the prostate.

TABLE III
Initial Symptoms Occurring in 280 Cases of Cancer of the Prostate

Symptom	Number	Per cent.
Frequency.....	134	47.8
Difficulty.....	96	34.2
Nocturia.....	79	28.2
Dysuria.....	60	21.4
Retention.....	45	16.0
Backache.....	26	9.2
Hæmaturia.....	24	8.5
Pain in thighs and legs.....	19	7.5
Pain in lower abdomen.....	14	5.0
Urgency.....	12	4.2
Incontinence.....	11	3.9
Constipation.....	10	3.5
Pain in hips.....	9	3.2
Loss of weight.....	8	2.8
No urinary symptoms.....	8	2.8

Usually patients presented three or more symptoms at the onset, which caused them to consult a physician. The most common triad was that of frequency, difficulty and nocturia. Many patients waited, however, until retention or hæmaturia compelled them to seek advice. Retention in itself is not indicative of far-advanced cancer. It is often caused by associated benign hypertrophy. Diligent search for carcinomatous changes in the prostate of the retentive case will often lead the surgeon to an early diagnosis of prostatic carcinoma. Many of our patients' histories indicate the possibility of much earlier diagnoses had their physicians made careful digital examinations at the time of the first attack of retention. In our series, an average of twenty-four months had elapsed between the appearance of initial symptoms and our first examination. Hæmaturia, on the other hand, is seldom an early symptom, usually occurring only when the tumor has invaded the posterior urethra or bladder. Twenty-four or 8.5 per cent. presented hæmaturia as the initial symptom and thirty-nine or 13.9 per cent. as a subsequent symptom. Hence a total of sixty-three had hæmaturia at some time in the course of the disease, cystoscopic examination proving forty-one of these to have extension of the neoplastic process to the bladder.

Occasionally there are no urinary symptoms in well-advanced cases of prostatic cancer, as in eight of our patients. In these eight the symptoms were referred to the gastro-intestinal tract and the genital organs. One consulted his physician because of persistent diarrhœa. Another because of

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rectal bleeding for which he was subjected to hæmorrhoidectomy, the true nature of his disease becoming apparent only after the failure of the operation to relieve his symptoms. A third complained of curved erections of the penis over a period of three years, due to direct invasion of the corpora by prostatic cancer. The fourth had a colostomy and later a resection for supposed rectal carcinoma before the tumor was shown to be of prostatic origin. In a fifth, resection of the right ileum was undertaken for a new growth which proved to be a metastasis from a cancerous prostate. The sixth and seventh suffered operative attacks on various metastatic lesions of the disease, while the last complained of incontinence of fæces due to invasion of the sphincter ani by the tumor.

The later symptoms of cancer of the prostate do not differ greatly from the initial symptoms. Urinary symptoms and pain are the most important, nocturia, retention and hæmaturia leading the list. A tabulation of these and other later symptoms in our series of 280 cases follows:

TABLE IV

Secondary Symptoms Occurring in 280 Cases of Cancer of the Prostate

Symptom	Number	Per cent.
Nocturia.....	51	18.2
Retention.....	45	16.0
Hæmaturia.....	39	13.9
Frequency.....	34	12.1
Dysuria.....	32	11.4
Loss of weight.....	31	11.0
Backache.....	25	8.9
Loss of strength.....	20	7.1
Pain in thighs and legs.....	18	6.4
Pain in lower abdomen.....	14	5.0
Constipation.....	13	4.6
Rectal pain.....	10	3.5

Less frequent symptoms occurring late in the disease referred chiefly to the incidence of distant metastases or to regions unrelated to the urinary tract.

Early Diagnosis and Biopsy.—It seems superfluous to state that earlier diagnosis is of prime importance, yet with twenty-four months on the average elapsing between the onset of symptoms and the establishment of the diagnosis in the patients represented in this series, the point can stand vigorous emphasis. We⁹ have stressed previously the importance of routine examination of the prostate in all men over fifty years of age. We would now add that the persistent exhibition of frequency, difficulty in urination, nocturia and retention in any patient of cancer age calls for a most careful and painstaking search for prostatic carcinoma.

The difficulties of accurate diagnosis of prostatic neoplasms have been considerably decreased by the adoption of biopsy by needle puncture and aspiration according to the technic of Martin and Ellis¹⁰ and applied to the prostate by one of us.¹¹

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In the series of cases here reported, 280 in number, there was histological confirmation of the clinical diagnosis by some form of biopsy or surgical specimen in forty-nine. This represents 17.5 per cent. of the total. Since the addition of biopsy by needle puncture and aspiration to our routine examination, except in those cases going to operation, we have secured histological evidence of our diagnosis in fourteen of the fifteen cases admitted. In five the specimen was obtained by Young's punch, while in nine the tissue was secured by our new biopsy technic. In one case no attempt at biopsy was made. Moreover, biopsy by aspiration has enabled us to secure important information in several older cases. In one a recurrence after four years of

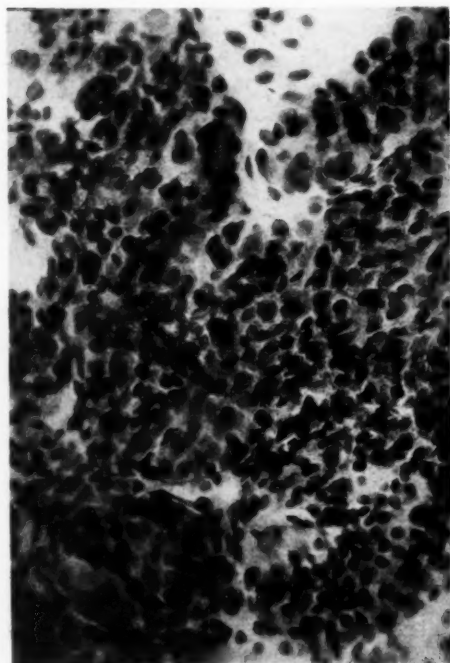


FIG. 1.—Specimen of tissue aspirated from far-advanced adeno-carcinoma of the prostate.



FIG. 2.—Specimen aspirated from small recurrent nodule. Adeno-carcinoma of the prostate under apparent control by radiation four years.

apparent control was proven; in another previously regarded as chronic interstitial prostatitis a carcinoma was demonstrated. Among the more recent cases, this form of biopsy enabled us to make a diagnosis of cancer in two early cases previously regarded as benign. In another a rare prostatic tumor was diagnosed in advance, and later proven at operation, by means of this procedure. Figs. 1 to 4 illustrate some of the above-mentioned cases together with the amount and character of the tissues obtained by needle puncture and aspiration. If we are seeking earlier diagnoses of these tumors it must be recognized that carcinoma may and does originate in any portion of the organ, regardless of the presence or absence of benign hypertrophy, and that no false sense of security should be felt due to apparent normality of the posterior

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lobe. By utilizing this advance in biopsy technic any suspicious nodule in the prostate may be readily subjected to microscopic study.

Treatment by Radiation.—A review of the use of radium and X-rays in carcinoma of the prostate at the Memorial Hospital reveals the difficult situation we are called upon to meet. An estimate of the status of 241 of the 280 cases here reported, made at the time of our first examination in each case, shows that 221 were classified as advanced cases while only twenty could fairly be classed as early cases. Seventy-eight of the 221 represented post-operative recurrences.

In spite of the far-advanced type of case coming to our service, we were



FIG. 3.—Small cell adeno-carcinoma of prostate. Clinical diagnosis difficult, proven by aspiration biopsy.

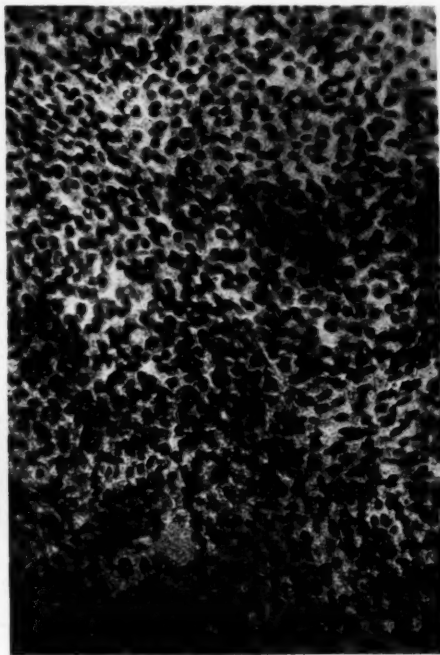


FIG. 4.—Adeno-carcinoma of the prostate. Early clinical case at first regarded as benign. Proven carcinoma by aspiration biopsy.

able to report five of forty-six cases alive and well after five years.¹² These forty-six patients constituted our first series and were treated between October, 1915, and January, 1917. In but one case was the neoplastic process confined to the prostate. No gross evidence of active cancer remained in the five patients surviving the five-year period, as far as we could see. These cases were treated by the insertion of steel radium-bearing needles through the perinæum into the prostate and seminal vesicles. Small doses, 200 to 300 millicurie hours for each needle, were utilized, repeating the dose every two to three months until the condition was controlled or no evidence of regression was found. In this way we were certainly able to control some cases as we have the autopsy record of one patient in this group who died from other

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causes seven years after first seen. The original tissue diagnosis by Doctor Ewing was carcinoma of the prostate. At autopsy no carcinoma was to be found.

Since that first series progress has been slow but sure. Our therapeutic routine has had to be changed frequently in order to avail ourselves of the advantages of newer methods and agents. Glass seeds of radon, low voltage and then high voltage X-rays, the radium element pack, radon filtered by platinum and now gold seeds of radon have all been used alone and in various combinations. We are gratified, however, that in spite of the necessity for the continual transition of radiation therapy, inspection of our file of current cases shows eight of forty patients alive and well for periods over five years. This means that 20 per cent. of our active cases are still under control after five years as compared with 10.8 per cent. in our first reported series.

We believe that in most cases of prostatic carcinoma a much larger dose of radium than heretofore used is necessary to control the disease. In other words, doses comparable to those we have used in controlling bladder carcinoma. The results of radium implantation in bladder tumors have consistently improved and are considered by us to be quite superior to operative resection.

We believe that a tissue dose of somewhere between 10 and 15 skin erythemas delivered to the tumor is necessary to control the large majority of prostatic carcinomata. The average adenocarcinoma is a radio resistant tumor but doses comparable to the above are sufficient for control in other locations and will undoubtedly prove so in cancer of the prostate. Since tissue dosage delivered to these tumors by external means alone, *i.e.*, high voltage X-rays and the radium element pack, can rarely exceed 1 to 1½ S.E.D., it becomes essential to deliver the bulk of the total dose necessary by interstitial radiation with gold seeds of radon. Because of this necessity for a large dose of radon accurately placed within the prostate we have quite reversed our original contention that the best approach was through the perinæum. We believe that cystotomy should be done, any obstructive portions of the prostate removed with cutting forceps or cautery, and the entire tumor, no matter what its limits, implanted with radon using seeds of 2 millicuries each to every cubic centimetre of new growth. In this way we are able to use doses adequate to the need, at the same time making the patient more comfortable and avoiding the risk of renal decompensation due to obstruction at the bladder neck. It seems to us that the suprapubic exposure is better suited to the purpose than the perineal route as that region is allowed to remain intact, securing its value as a protective barrier to tumor extension.

SUMMARY

There is no general agreement among urologists as to the best therapy for carcinoma of the prostate.

It is held that the possibilities of radical surgery are exhausted, certain

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features in the natural history of the disease precluding the effective application of this form of treatment.

It is shown that there has been gradual improvement in the control of carcinoma of the prostate by radiation.

The age incidence and symptoms displayed in a series of 280 cases of carcinoma of the prostate are tabulated.

The early diagnosis of the disease is discussed and the use of a new biopsy technic is suggested.

Treatment by radiation is discussed. Higher tissue doses and cystotomy are believed essential to the more effective control of prostatic carcinoma.

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SOME COMMONER DIFFICULTIES IN DIAGNOSIS AND TREATMENT OF CARCINOMA OF THE RECTUM AND COLON

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THIS discussion is based upon an analysis of 224 cancers of the rectum and colon, collected through the Cancer Division of the Department of Health of the City of Detroit.† It represents practically all of the cases treated in the Detroit hospitals for a period of two years and two months—May, 1927, to July, 1929. In addition, thirty-six cases of cancer of the colon, collected from the University of Michigan Hospital records* are added, making a total of 260 cases.

Data of this sort do not always lend themselves to an accurate analysis of symptoms, and the scattered auspices under which treatment was carried out does not lead to constructive analysis of methods. Neither of these was attempted. This study has been concerned with the commoner difficulties in early diagnosis; the early symptoms recorded on the hospital charts; the difficulties in X-ray diagnosis; a brief exhibit of treatment; and some of the problems in treatment as shown by these records.

The 224 cases collected from Detroit hospitals include, with a few possible exceptions, the entire experience of the hospitals in Detroit for two years and two months in cancers of the colon and rectum. During this time 350 persons were registered as having died of cancer of the colon and rectum, so that those treated in hospitals represent 65 per cent. of the total deaths (Table I).

TABLE I
Number of Cancers of Colon and Rectum Studied

	Detroit hospitals	Univ. Hosp., Ann Arbor	Total
Rectum.....	73	0	73
Rectosigmoid.....	32	8	40
Sigmoid.....	46	11	57
Descending colon.....	10	3	13
Splenic flexure.....	6	3	9
Transverse colon.....	14	6	20
Hepatic flexure.....	10	2	12
Cæcum and ascending colon.....	21	3	24
Colon.....	8	0	8
Appendix.....	4	0	4
Total.....	224	36	260

* For the privilege of using these records, we are indebted to Dr. Frederick A. Coller, Director of Surgery, University Hospital, Ann Arbor, Michigan.

† Through the courtesy of Dr. Chas. E. Dutchess, Director.

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Tables II and III contrast the Detroit hospital's incidence of rectum and colon cancer with the incidence as obtained from death certificates over a period of two and one-half years. For comparison, the incidence over five years at the University Hospital, Ann Arbor, is given.

It shows:

(1) Hospital incidence in Detroit agrees quite well with death-certificate incidence, except in the percentage of rectosigmoid growths and transverse colon, both of these being greater in the hospital series. The death certificates had 25 per cent. unclassified cases (death due to cancer of the colon, exact anatomical site not determined), compared to 3½ per cent. in hospital cases.

(2) The table from Ann Arbor shows a very high comparative incidence of rectal cancers. Perhaps the reason is that these cases, since they do not so generally develop obstruction, are more apt to be able to travel.

TABLE II

Carcinoma of Colon and Rectum. Hospital Incidence Compared to Death Certificate Incidence

	Deaths—Detroit Department of Health—3 years, 1927-28-29		Detroit hospitals— 2½ years		University Hospital, Ann Arbor— 5 years	
	No.	Per cent.	No.	Per cent.	No.	Per cent.
Rectum.....	125	33.9	73	32.6	138	62.4
Rectosigmoid.....	13	3.6	32	14.3	5	2.2
Sigmoid.....	77	20.9	46	20.5	29	13.1
Descending colon.....	6	1.6	10	4.5	8	3.6
Splenic flexure.....	5	1.4	6	2.7	5	2.3
Transverse colon.....	10	2.7	14	6.2	7	3.2
Hepatic flexure.....	7	1.9	10	4.5	1	0.5
Cæcum and ascending colon.....	33	8.9	21	9.4	17	7.7
Colon.....	91	24.8	8	3.5	11	5.0
Appendix.....		.3	4	1.8	0	0.0
Total.....	367	100.	224	100.	221	100.

TABLE III

Incidence

	Death certificate— Department of Health—3 years	Detroit hospitals	University Hospital, Ann Arbor	Yeoman's series
No. of cases.....	215	151	172	88
Rectum.....	58.1	48.3	80.3	31.8
Rectosigmoid.....	6.0	21.2	2.9	22.7
Sigmoid.....	35.9	30.5	16.8	45.5

Table III shows the per cent. incidence estimated for rectum, rectosigmoid and sigmoid only, with a table from Yeoman's Proctology* for comparison. Evidently, from these two tables, there are fewer rectosigmoid cancers re-

* Yeoman's Proctology. Appleton, p. 498, 1929.

ported in death certificates than one should expect from the hospital incidence of growths in this anatomical site. The reason is not clear.

SYMPTOMS

Of the 260 cases, information concerning the duration of symptoms before diagnosis, the first symptoms complained of, and whether or not there was obstruction at the time of operation (or diagnosis) was obtained in 213. These are charted in Table IV. These cases came to operation from 6-12 months after the onset of symptoms; the shortest being splenic flexure, 5.9 months, the longest, rectosigmoid, 13.2 months. At the time of operation (or diagnosis) 40-75 per cent. showed obstruction, either chronic or acute (excepting rectal and caecal growths, where obstruction is not prominent). As will be noted later, this is much too late for good results from treatment. All are agreed that earlier recognition would contribute more to better results than any other factor. Hence the importance of early, or first symptoms.

Rectum.—It is evident that, in this series, bleeding from rectum—the commonly known symptom of rectal cancer, was noted as the first symptom in only one-third of the cases. The usual rectal carcinoma is the adenocarcinomatous ulcer in the ampulla. Following a symptomless period during which the tumor must be small, there is a well-recognized stage during which symptoms are chiefly tenesmus, pain, or discomfort in the region of the rectum. It is only later, when ulceration develops, that bleeding takes place. Almost half of these cases started with tenesmus, pain in the rectum, or diarrhoea (sometimes bloody or blood streaked, but chiefly diarrhoea). Bleeding (except as blood-streaked diarrhoea in which the diarrhoea was the patient's chief complaint) was generally noted as starting 1–3 months after these symptoms of rectal irritation. A few started with increasing or suddenly appearing constipation, a few with the sensation of a mass. Gas in the bowel—distention—is not a very common symptom of the onset of rectal cancer. Often where this was noted as the initial symptom, further study showed the anatomical location to be the rectosigmoid junction or sigmoid rather than the rectum proper.

From our records, it is doubtful whether these pre-ulcer symptoms are generally looked upon by either the patient or the attending physician as of possible serious significance. The cases, however, seem to be recognized in the bleeding stage. Very few were noted as having obstruction. We have records of only two cases where hæmorrhoidectomy was done (both by medical irregulars), and two others where medical treatment was given during the time in which the patient had symptoms of cancer.

Rectosigmoid.—Here one-fourth started with rectal bleeding as the first symptom. About half started with symptoms of constriction: obstinate constipation (either from previous mild constipation or from previous health), or symptoms of irritation—diarrhoea, alternating diarrhoea and constipation, tenesmus, *etc.* The remainder started with left lower abdominal pain, loss of weight and weakness, *etc.* Blood was usually present in the stools after

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TABLE IV
First Symptoms Complained of by 213 Patients with Cancer of the Rectum and Colon

Total number	Per cent. obstruction at time of diagnosis or operation	Average duration of symptoms before diagnosis, mos.		Bleeding	Diarrhoea	Pain in rectum, bearing down, pain, tenesmus, etc.	Obstinate constipation	Mass in rectum	Altering constipation and diarrhoea	Lower abdominal pain	Subacute or acute obstruction	Right lower quadrant pain	Loss of weight, or weakness	Mass in abdomen	Pain in back	No symptoms
66	0	0.1	Rectum.....	23	13	15	7	3	2	3	1				1	1
30	41.6	13.2	Rectosigmoid.....	8	5	1	6			3	9		4			
43	60.8	7.2	Sigmoid.....	6	2	1	8			13	2					
12	41.6	11.7	Descending colon.....	2			5			3	1					
9	77.1	5.9	Splenic flexure.....	3	1		1		2	4						
10	68.4	11.1	Transverse colon.....						1	13		1				
11	60.	9.4	Hepatic flexure.....							6		2	2			
19	12.5	11.2	Cecum and ascending colon.....				1			5		11		2		
4	.0	8.3	Appendix.....							1		3				
213			Total.....	42	21	17	29	3	5	51	14	17	10	2	1	1

TABLE VIII
Comparison of Recoveries and Post-operative Deaths from Resections of the Rectum and Colon for Cancer

Fixation; extent; metastases at time of operation	Recovery					Resections	Death						
	Second stage removal	Resection, first stage	Preliminary colostomy	Obstruction	Average duration of symptoms	Number	Number	Average duration of symptoms	Obstruction	Preliminary colostomy	Resection, first stage	Second stage removal	Metastases at time of operation
11	7	9*	7	0	5.8	16	14	8	0	5	9†	5	4
0	2	2	1	1	20	6	3	18	3	1	3	1	2
3	4	1	1	4	12	16	16	0.4	11	7	8	7	3
2	0	4	0	2	8	4	7	5	1	0	7	0	1
1	2	1	3	1	7	4	7	0.5	1	2	4	1	6
						Total.....	49						

* Perineal resections.
† Five abdominal perineal, four perineal resections.
‡ Not definite.

the lesion had existed for 2-3 months and there was a frequent note of subsequent gaseous distention, lower abdominal distress, *etc.*, but not necessarily of symptoms of obstruction.

Sigmoid and Descending Colon.—Here lower abdominal pain and distress, and obstinate constipation are the predominating first symptoms. Of fifty-five cases of both sigmoid and descending colon, sixteen started with abdominal pain and distress—sometimes mild bloating, sometimes sharp colicky attacks; thirteen with obstinate constipation and eleven with attacks of subacute or acute obstruction. Of the remaining fifteen, eleven started with rectal symptoms—bleeding, diarrhoea, tenesmus, *etc.*—and the remainder (four) with loss of weight and weakness. Evidently the abdominal pain is not always suspected of being due to sigmoid cancer. It was described as vague dyspepsia and abdominal distress simulating an upper abdominal lesion just as often as “lower abdominal pain.” Only occasionally was it noted as pain to the left of the umbilicus. The majority of these sigmoid growths which started with vague pain or obstinate (or increase in) constipation, shortly developed attacks of subacute obstruction. As noted, eleven started with attacks of suddenly appearing obstruction. Several cases gave histories of such attacks, with distention and sometimes vomiting for 3-5 months before the diagnosis was made. In some cases patients were admitted to hospitals, then discharged in a few days after the attack subsided.* One case had an operation for inflammatory disease of the adnexa during the course of the symptoms. As noted, blood in the stools is a less frequent early warning than is the careful investigation of lower abdominal pains. When present, of course, it is definite. All authorities mention its early importance. The charts also left the impression that earlier local examination by proctoscopy and sigmoidoscopy would be of considerable value.

Splenic Flexure, Transverse Colon.—The symptoms here are similar. Blood in the stools ceases to be an early symptom after the splenic flexure is passed, and the abdominal distress is of most importance. It was described as flatulent bloating, lower or general abdominal pains and distress, cramps in the abdomen or severe colicky pains. The importance of careful anamnesis is great—for 60-80 per cent. of these cases have obstruction when they finally come to operation, and the early symptoms, probably due to spasm of the bowel at the site of constriction, are regularly unrecognized. In a few cases, a so-called phantom tumor was felt, which disappeared immediately, giving a false sense of security. Subsequent events showed that these were probably faecal impactions proximal to the site of constriction, and as the oedema, *etc.*, at this site subsided, the tumor disappeared. The colon can accommodate itself to marked degrees of narrowing and produce only very mild symptoms. A diet for spastic constipation may give complete relief. Alvarez records a patient who lived for years in relative comfort on a bland diet, with an unus-

* “It is rather disturbing to find patients being sent out from hospitals because the X-ray shows no lesion, and in spite of the fact that there is a typical history of cancer of the colon or rectum . . .” Jones, Daniel F.: *ANNALS OF SURGERY*, vol. xc, No. 4, p. 675, October, 1929.

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pected stricture of the colon, then suddenly developed acute obstruction with perforation when a small bit of lettuce lodged in the narrowed area. In two cases, abdominal pain caused by early malignant strictures were so mild or atypical as to be diagnosed intestinal flu.*

Hepatic Flexure, Ascending Colon, Cæcum.—The early pains due to carcinoma at the hepatic flexure were not so frequently confined to the right side of the abdomen as one would think; six complained of lower abdominal pain, two of right lower quadrant pain. Obstruction is not so prominent; the growths attain large proportions, and are sometimes confused with gall-bladder disease—symptomatically, on examination and by röntgenography.

The pain in cæcal and ascending colon growths was chiefly confined to the right lower quadrant. In two cases the first symptom was a mass suddenly appearing on the right side.

Appendectomy was done during the course of the symptoms once for cæcal cancer, once for hepatic flexure and once for transverse colon growths. One case was operated upon for ovarian cyst and a cancer in the region of the cæcum discovered.

In summary, some of the problems in the early recognition of rectal and colon cancers, as revealed by this brief study of 260 cases collected in an average manner are:

(1) Perhaps two-thirds of all rectal cancers have an early period in which symptoms are chiefly tenesmus, pain on defecation, ache in lower sacral region, *etc.*, before there is blood in the stools. This is not generally recognized.

(2) In growths of the colon proper, patients had lower abdominal distress, ranging from mild flatulence with or without nausea to severe colic, for several months before diagnosis.

(3) Several patients had attacks of subacute obstruction for months before cancer of the colon which caused them was recognized.

(4) At the time of diagnosis or operation, 60–80 per cent. of splenic flexure and transverse colon growths were obstructed; 40–60 per cent. of the hepatic, descending, and sigmoid and rectosigmoid. Ascending and rectal growths showed very little obstruction.

(5) A few rectal cancers had hæmorrhoidectomy or medical treatment for hæmorrhoids, a few right colon growths had appendectomy during the course of symptoms. From these records the number is probably less than the usually reported 10–15 per cent.

X-ray.—There is a tendency, especially in the average practice of medicine, to attach considerable importance to an X-ray examination. The clear visual picture, the typewritten report, are certainly more demonstrative than the painstakingly obtained history of vague abdominal distress, which often depends for its accuracy upon "that delicate adjustment between a nervous patient's recital of symptoms and a physician's powers of analysis." The

* Starr, Frederick N. G. (ANNALS OF SURGERY, vol. xc, No. 4, p. 687, October, 1929), remarked that during 1928 he had seen twelve patients with cancer of the rectum and colon "who dated their ill health to an attack of what had been called 'intestinal flu.'"

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fact that the röntgenogram is only a shadow, subject to certain limitations in the demonstration of physiological and pathological processes, may perhaps be worthy of repetition.

Table V shows the total number of cases studied, the number who had no X-ray, and those where there was no note of X-ray examination, in the first three columns. The next three columns show the number of positive X-ray diagnoses, negative reports, and an interesting group in which the X-ray was indefinite or indeterminate. The last column records the percentage of the total number examined in which X-ray was negative or indeterminate. Rectal cancers are not included, since few X-ray examinations were made of these cases.

TABLE V
X-Ray Examinations

	Total No. studied	No X-ray	No note	X-ray positive	X-ray negative	X-ray indefinite and indeterminate	Per cent. X-ray negative and indeterminate
Rectosigmoid.....	39	9	9	17	2	2	19.0
Sigmoid.....	51	10	12	25	1	3	13.8
Descending colon.....	12	1	0	10	1	0	9.1
Splenic flexure.....	9	1	1	5	1	1	28.6
Transverse colon.....	19	2	4	9	0	4	30.8
Hepatic flexure.....	12	0	3	5	0	4	44.4
Cæcum and ascending colon.....	20	3	4	10	2	1	23.1
Appendix.....	4	3	0	0	0	1
Total.....	166	29	33	81	7	16	22.1

In this series there is an error of 22 per cent. in X-ray examinations, *i.e.*, in that number of proved cancers of the colon and rectosigmoid the X-ray was either negative or indeterminate. A greater percentage of error was made in hepatic—transverse—splenic flexure growths than in descending and ascending colon tumors. In most of the reports where indeterminate diagnoses were given, a spasm or irregular filling defect was noted—sometimes present on one examination, absent on another. In one or two cases, this spasm was present above the tumor in one examination and below in another, the region of the tumor showing no change. This corresponded with palpable tumors present at one time and not at another. Sometimes the delay in stomach and small bowel was noted, but the interpretation was that it was due to a lesion other than carcinoma of the colon—"pancreatic neoplasm"—"obstruction in small bowel," etc.

Two hepatic flexure growths were thought to be more diffuse than cancer—probably tuberculosis or diverticulitis. Another confusion lay in interpreting a smooth walled appearance of the colon, with absence of haustrations, as due to ulcerative colitis, when this flattening was due to the constriction of a growth higher up, which itself could not be demonstrated. All these difficulties probably are due to the fact that the colon very frequently can accommodate itself to quite marked narrowing of its lumen, and still allow the

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passage of the normal faecal current. They are errors in the method, which must be appreciated—the barium shadow can show only the function at the time of examination and is not a mirror of the entire pathological physiology of the bowel.

Another source of confusion lies in the fact that the early symptoms which may denote subacute large bowel obstruction—gas, bloating after meals, distention, *etc.*—passing off without much actual pain, frequently simulate distress due to chronic cholecystitis. An X-ray examination showing a non-filling gall-bladder gives a sense of security; the diagnosis of a comparatively mild intra-abdominal condition contributing to delay in treatment. In two cases X-ray of the gall-bladder only was ordered. In one of these gas in the small bowel was noted—shown at operation to be due to cancer of the caecum.

The negative and indeterminate X-rays are detailed in Table VI.

TABLE VI

X-Ray Indeterminate

Rectosigmoid	X-ray.—Slight irregular rectosigmoid spasm or extragastric pathology. Medical diagnosis.—Hodgkin's disease or cholecystitis. Proctoscopic examination.—Cancer rectosigmoid. Operation.—Inoperable cancer rectum.
127151	
2028	X-ray.—Ulceration at junction of descending colon and sigmoid. Operation, also proctoscopy.—Mass size fist at rectosigmoid.
Sigmoid	X-ray.—Spasm rectosigmoid junction. No organic pathology. Operation.—Colostomy for cancer sigmoid.
142531	
214533	Fluoroscopic negative. First films show constriction, second barium enema negative, third enema adhesions or neoplasm narrowing sigmoid. Medical diagnosis.—Duodenal ulcer. Another X-ray also thought duodenal ulcer. Operation.—Cancer sigmoid.
158950	X-ray.—Questionable defect lower sigmoid. "Believe spastic rather than organic." Operation.—Cancer sigmoid.
Splenic	X-ray defect seen first in transverse colon, then at a second examination seen in descending colon. At operation no tumor found. Colostomy for supposed colitis. Post-operative treatment.—Colitis. Death five and one-half months later. Autopsy.—Cancer splenic flexure.
124366	
Transverse	X-ray inconclusive. Irregular filling defect not constant. Medical diagnosis vitamine deficiency. Autopsy.—Cancer transverse colon.
Colon	
201832	
2333	X-ray.—"While appearance still not typical of malignancy, we think there are indications for laparotomy." Operation.—Typical constricting cancer transverse colon found.
3335	X-ray.—Non-descent caecum. Delay in small bowel. Partial obstruction in small bowel. At operation.—Annular cancer transverse colon. Microscopic.—Adenocarcinoma.
2329	X-ray in 1925, seventeen months before operation, taken because of belching gas, diagnosed gall-stones. Operation, 1927.—Obstruction mid-transverse colon. Carcinoma.
Hepatic	"While at first we thought there was a definite cancer at right end of transverse loop of colon, repeated examinations make us consider a varying process such as diverticulitis or tuberculosis. Second X-ray against cancer—in favor of tuberculosis. Operation.—Large cancer hepatic flexure.
2341	

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2342	X-ray.—Chronic obstruction hepatic flexure. Infiltrating lesion, probably old tuberculosis. Operation.—Large mass upper right, which proved to be cancer of hepatic flexure.
2317	X-ray.—Entire colon normal caliber. No haustration—may be due to ulcerative colitis. Non-filling gall-bladder. Operation.—Massive hepatic flexure cancer. No microscopic.
2343	X-ray.—Redundancy in descending colon, probably due to mucous colitis of large bowel. Slight erosion of the duodenal cap suggests ulcer. Second examination one week later: constriction in sigmoid suggests new growth in this region. Operation.—Cylindrical obstructing cancer at hepatic flexure.
Cæcum 971	Gastro-intestinal X-ray. Narrowing of transverse colon five inches from hepatic flexure, 1 inch in length, may be due to adhesions or probably cancer. Barium enema, partial obstruction at the point just distal to hepatic flexure. Diagnosis undetermined; does not look like cancer. Operation.—Resection for cancer cæcum.
551	Films of gall-bladder show marked gaseous distention of cæcum, ascending and transverse colon with some gas; also seen in terminal loops of ileum. No evidence of gall-stone shadows. Operation.—Appendiceal abscess, possible malignancy. Pathological.—Advanced adenocarcinoma. X-ray negative.
Rectosigmoid 1351	Gastro-intestinal. X-ray negative. Stomach, duodenal ulcer, small bowel. Operation one month later.—Large mass posterior wall recto-sigmoid junction.
190588	X-ray absolutely negative. Patient died two months later. Autopsy.—Cancer rectosigmoid.
Sigmoid 2118	X-ray.—No definite lesion in colon present. Operation.—Sigmoid adherent in pelvis and contained a carcinomatous mass size of a lemon.
Descending colon 1370	X-ray.—Constriction sigmoid, but on repeated examination after atropin no deformity was noted. One month later acute obstruction. Operation.—Annular cancer sigmoid. Autopsy.—Annular cancer descending colon.
Splenic flexure 2320	Cancer colon suspected clinically. X-ray, no growth. Operation for acute appendicitis nineteen months later. Malignancy splenic flexure found.
Cæcum 2350	X-ray.—Marked twenty-four-hour gastric retention not explained by lesion in stomach, but from pressure from without—might result from cancer of pancreas. Forty-eight hours later there is still a gastric residue. Large bowel well outlined. No defects in colon. Autopsy.—Cancer cæcum.
500x	X-ray.—Obstruction pylorus—complete—suggests pancreatic neoplasm. Autopsy three or four days later—ileocæcal cancer.

TREATMENT*

Table VII lists the treatment of all cases with recovery and deaths of those operated upon.

* These analyses of treatment include only Detroit hospital cases. As stated above (page 1), it was difficult, in cases collected in this manner, to be sure that all charts were included. A careful recheck showed that very few records of patients who had had resections were omitted. Several colostomies, ileostomies and exploratory laparotomies, where the final diagnosis was not definitely established (no X-ray, operative note not positive, etc.), purposely were not studied. The tables in this section, therefore, are meant to illustrate only the observations made, and are not an exact record of the total number of cases treated or observed during the time period covered by this study.

CARCINOMA OF RECTUM AND COLON

The chief practical importance lies in those cases where resection was attempted—where treatment offered a chance of cure. Table VIII contrasts certain data in the resected cases who recovered and in those who died after operation.

TABLE VII
Treatment of 222 Cases of Rectum and Colon Studied

	Resection		Colostomy; cæcostomy; enterostomy		Ileostomy; sigmoidostomy		Exploratory laparotomy		No treat- ment	Total
	Recov- ery	Death	Recov- ery	Death	Recov- ery	Death	Recov- ery	Death		
Rectum.....	16	14	9	5					23	67
Rectosigmoid...	4	5	7	4					5	25
Sigmoid.....	6	16	0	11		2		2	5	42
Descending colon	11	7	2	3		3	1	1	5	33
Splenic flexure..										
Transverse colon										
Hepatic flexure..	11	7	1	2	1	1	2	2	3	30
Cæcum and as- cending colon.										
Colon unclassi- fied.....						1	1			2
Appendix.....							4			4
Diagnosis not definite...							8		11	19
Totals.....	48	49	19	25	1	7	21		52	222

Rectum.—These cases are characterized by the fact that there is little obstruction present, and that a large number—almost one-third—are so far advanced when diagnosed that they are refused operation. The cases where death followed resection had had symptoms two months longer than those who recovered from resection; yet even of those who recovered, eleven of sixteen—almost three-fourths—had an operative note that the growth was already fixed, or had extended to contiguous tissues, or had metastasized. Many of those who recovered from resection died within a few months. Evidently operation must be done sooner than six months after the onset of symptoms to be satisfactory in many cases.

Concerning methods, except for the high mortality following the combined one-stage abdomino-perineal resections, the table shows nothing remarkable as regards type of operation, preliminary colostomy, *etc.* The colostomies did not seem to be done for acute obstructions so frequently as in growths higher up, but more generally as a first exploratory stage, with contemplated radical removal later.

Colon.—Apparently most of these cases are operated upon sooner or later—probably because so many end finally in obstruction or severe attacks of abdominal cramps. The mortality from resections is high. In general,

the cases who died following resection do not show longer duration of symptoms, more obstruction, or fewer preliminary decompressive colostomies than those who survived. Also, the operative notes concerning fixation, extension and metastasis are no more frequent in the deaths than the recoveries. The numbers are probably too few, the auspices too scattered for accurate analyses.

Rectosigmoid.—These growths have a long period of pre-operative symptoms—eighteen to twenty months—three times as long as rectal cancers—before diagnosis or operation. Much more relief is obtained by colostomy here than by colostomy for sigmoid growths a short distance higher, and it is done with much lower mortality.

Sigmoid.—In this series the mortality from resections is quite high. Where only colostomy was done, the mortality was 100 per cent. (eleven colostomies, eleven deaths). Most of these cases had marked obstruction. On the subject of colostomy in these cases Dixon* has recently expressed himself as follows: "I believe that in cases of carcinoma of the sigmoid and rectosigmoid enterostomy is usually unnecessary. If frequent enemas and hot abdominal stupes are used the carcinoma will usually relax sufficiently to allow the contents of the intestine to pass through." Probably many of these cases were in greater extremis than patients who might be able to travel before being operated upon; yet a perusal of the charts leaves the impression that pre-operative cleansing over a period of several days is not so thoroughly carried out as Dixon, Rankin and others recommend. The operative notes in these cases, also descending and transverse colon, left the impression that the growths are not extensive—certainly not when compared to rectal cancers of the same duration of symptoms—and if removal could be accomplished satisfactorily, a favorable prognosis might be given.

Splenic Flexure.—All of these cases died—either following resection, colostomy or exploration. Cancers of the splenic flexure are noted for their high mortality, to which their inaccessible position contributes, and for their insidious onset, frequently being very difficult to recognize. Though some authors state that all have obstruction, some cases go on to perforation with symptoms only of left costal pain, left subphrenic abscess. In one case in this series an unsuspected abscess contiguous with the growth in the left subphrenic region was entered at the time of operation.

Cæcum, Ascending Colon.—Most of the hepatic and cæcal tumors were already large masses by the time they came to operation. The technical difficulties of extensive resections of the right half of the bowel are apparent. The experience here with short circuiting operations—ileo-sigmoidostomy, etc., was not good. Rankin has also noted that this operation short circuits the water absorbing portion of the bowel, and the ensuing diarrhoea contributes to the dehydration and post-operative toxæmia. He has recommended preliminary ileostomy several weeks in advance, so that the water loss can become adjusted.

Cause of Post-operative Death.—An analysis of post-operative causes of

* Dixon, C. F.: Proceedings Staff Meetings Mayo Clinic, vol. v, p. 107, April 16, 1930.

CARCINOMA OF RECTUM AND COLON

TABLE IX

Cause of Death Following Resection and Colostomy for Cancer of Rectum and Colon

	P.O. deaths		Peri- tonitis	Prob- ably peri- tonitis. Ob- struc- tion	Myo- cardial failure, shock	Pul- monary embo- lism	No note	Sudden hæmorr- hage	Chronic ne- phritis
Resections	13	Rectum		1	2		8		2
	4	Rectosigmoid.....	1	2			1		
	17	Sigmoid	6	6	1	1	1	1	1
	7	Descending splenic trans....	2	2	1	1	1		
	8	Hepatic ascending cæcum	1	3	1	2	1		
	49	Total	10	14	5	4	12	1	3
Colostomy ileostomy	5	Rectum					5		
	4	Rectosigmoid.....		2			2		
	11	Sigmoid	2	5	1		1	1	1
	1	Descending splenic trans...					1		
	2	Hepatic ascending cæcum					2		
	23	Total	2	7	1	0	11	1	1

death was attempted. In some cases an autopsy or post-operative wound inspection gave an accurate report. Frequently, however, only a rough clinical appraisal was possible, based upon the post-operative notes, nurses' record, etc. For example, a patient dying four, five or six days after operation exhibiting continuous abdominal pain, vomiting, distention, high evening temperature, and no respiratory signs was thought to have died of peritonitis. Twelve of seventy-two deaths following resection or colostomy were due definitely to peritonitis. Using the above clinical estimate, another twenty-one were thought to have died of peritonitis or bowel obstruction, making thirty-three of seventy-two deaths due to peritonitis, probable peritonitis or obstruction. Myocardial failure, shock, were thought to be responsible for six fatalities. Pulmonary embolism, chronic nephritis (or delayed exhaustion), four each, sudden hæmorrhage, two. No data were available in twenty-three cases.

The problem in treatment, therefore, resolves itself to a great extent into the problem of preventing peritonitis. Rankin† has elaborated upon this. The organisms in the colon are virulent, and are easily squeezed into adjacent tissues by operative handling, especially mobilization of an adherent growth. In addition to leakage from failure of coaptation, there may be necrosis due to inadequate blood supply, or post-operative distention may cause strain on the suture line. Pre-operatively reducing the local infection to a minimum by high caloric, scant residue diet for several days, and overcoming the anæmia and dehydration are most important. Pre-operative heightening of the body immunity with colon vaccine, aseptic resections, absolute post-operative bowel rest are aids.

THE PATHOLOGY ASSOCIATED WITH RUPTURE OF THE SUPRASPINATUS TENDON

BY ERNEST A. CODMAN, M.D. AND IRVING B. AKERSON, M.D.
OF BOSTON, MASS.

IT MAY seem out of place in discussing the above subject to give a brief history of the Registry of Bone Sarcoma, but since it is due to the existence of that Registry that this article is written by a surgeon in this special number of the *ANNALS OF SURGERY*, I feel that a few words of explanation are necessary. I am not a pathologist and have very little more claim than any other surgeon who learned his pathology in 1894 to entitle me to have an article in this number. My excuse in this instance is my association with Doctor Ewing on the Committee of the Registry of Bone Sarcoma. My interest in the pathology of bone tumors was aroused in 1920 by a case which came under my care. This patient was the wife of one of my best friends, a man of keen intelligence with a splendid regard for the plain truth. I told him how little there was known about bone tumors and how difficult it was to find any exact facts about cases which were claimed to have been cured. He offered to pay the expenses if I would undertake to write to all my surgical friends and find out if there actually were any cured cases of bone sarcoma. Before I had been able to run down many cases which had survived any kind of treatment long enough to be considered cures, my patient died. An autopsy revealed that the tumor was metastatic carcinoma and was not a primary sarcoma of bone.

Even after a pathologic specimen was obtained at autopsy there was still doubt of the diagnosis and in fact there still is, for no primary tumor was found at autopsy and the origin of the metastasis remains unsolved. These facts and those gleaned from my correspondence, demonstrated to me very clearly that the entire knowledge of the diagnosis and treatment of bone tumors was very obscure and of very little practical consequence to an individual patient. Meantime I had amassed so much correspondence concerning alleged cures from many of the most prominent surgeons and pathologists in the country, that it seemed a pity to give up the investigation even though it could never be of use to my patient. The result was the formation of the Registry of Bone Sarcoma which was financed by the American College of Surgeons.

The writer was appointed registrar with Dr. Joseph C. Bloodgood and Dr. James Ewing as the other members of the committee. At that time I was also inspired by the hope of making this one disease an example of what I had previously called the End-result System of Hospital Organization, in which for the previous decade I had been intensely interested as a member of the Committee on Hospital Standardization. I was willing to

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give up more than half my time to the Registry with the hope that in this one disease I could get all the hospitals in the country to record (*i.e.* register) whatever instances came within their doors. All I asked was a brief, truthful record of each case, with X-ray films and pathologic slides, and if the patient were treated, an annual notation of his condition. The data thus collected would be studied by our committee with a view to obtaining more satisfactory methods of diagnosis and treatment, and data were to be submitted to as many other pathologists as we could induce to study them. My interest in the success of the Registry was wholly in showing that it was possible (as a matter of human nature) for the surgical profession of this country to get together in giving a truthful account of what happened to patients afflicted with this one rare disease, even though the record of each case should be a record of error in diagnosis and treatment. If we could be sure that every hospital in the country was giving proper diagnostic facilities, proper X-ray technic and interpretation, proper pathological skill and knowledge, and judicious and skillful surgical treatment to cases with this one disease, we would at the same time be showing that they were capable of (and probably giving) a similar grade of service to other patients with other diseases. The ability to register a case was not only a criterion of the equipment and skill of a hospital staff, but also a criterion of its ability to coöperate and of its organization, because unless the organization of a hospital was of a high grade, sufficient pressure could not be used on any individual in a staff who had failed to diagnose or treat rationally one of these cases, so that he would permit publicity of the facts with a truthful account of his errors. Since errors in diagnosis and of judgment in treatment were the rule in cases of this lesion, no harm would be done.

From my point of view, the Registry of Bone Sarcoma has been a miserable failure. I was disappointed in the ability and zeal of the staffs of even the Class A hospitals to register their cases truthfully. Two of the greatest private institutions in this country would not coöperate. Naturally, with this illustrious example, many of the other hospitals shirked or failed to take the trouble to register their cases. However, a large number of hospitals (particularly those which were untrammelled by academic affiliations, by traditions of antipublicity or by consciousness of being business enterprises), registered their cases, so that in spite of the failure of the real purpose of the Registry, a considerable amount of data was accumulated for scientific study by the committee and interest in the study of bone tumors was generally aroused. That this material was used by Dr. James Ewing to complement and augment his already great knowledge and experience in this subject, saved the Registry from utter failure.

Everything that the Registry has really accomplished is due largely to the brain of Doctor Ewing. It was his guidance that led to the classification of bone tumors, which though admittedly imperfect, is now the accepted classification. Dissemination of knowledge about the form of round-cell sarcoma which has come to be called Ewing's sarcoma was accomplished very largely

by the Registry, but the separation of this tumor from the other bone sarcomas was made by Ewing even before the Registry had made any publication whatever. So while the Registry has helped, it was Ewing who brought the attention of the profession to the fact that this form of tumor is clinically an entity. The almost voluminous literature which has accumulated in consequence of the interest aroused by the Registry has been dominated for a decade by Doctor Ewing's thought. Kolodny's book, which is, at present, by far the most accurate presentation of our knowledge of malignant bone tumors, is admittedly an expression of Ewing's ideas. I feel that the best that can be said for the Registry is that it has helped to crystallize and diffuse the knowledge of bone pathology which James Ewing had accumulated during his previous years of study.

During my five years as registrar, I was in constant touch with Doctor Ewing. He painstakingly reviewed nearly every case which was registered, wrote his opinion at the time, and, in perhaps half the instances, reviewed the case a second time a year or more later to see if his opinion had been modified. He was a constant source of inspiration and encouragement to me as I labored over the detailed work, for I felt that my time was well recompensed in having the material which I had collected studied by him. In spite of his great knowledge and experience, some of his earlier diagnoses had to be corrected later, and I found him always ready to discuss all points made by other pathologists, and to give them due weight. He could modify his own opinion if the comments of the other pathologists enlightened it at all. I spent many hours with him discussing the cases and although he knew how limited my knowledge of pathology and histology was, he was always ready to listen to my opinion and suggestions. If he disagreed, he frankly said so. If I was able to show him something he had overlooked, he was quite ready to accept it. His frankness and patience in these long discussions were remarkable, for I know that I was taking his time from other valuable work. My duties as registrar brought me into intimate contact with many other pathologists and I learned that so far as bone tumors were concerned, no pathologist, even Ewing himself, had accurate knowledge. It was a subject on which "a cat might look at a king." My intensive study of these cases gave me an advantage, although I knew little of pathology in general, and I was able to see that so far as the histologic diagnosis of bone tumors was concerned, a surgeon who could interpret X-ray films and who knew the clinical story of the cases could make the diagnosis as accurately in most cases as the pathologist could with the average inadequate material which is given to him by surgeons from specimens taken at exploration. If the combined clinical and röntgenologic opinion was in doubt, it generally proved that the pathologist was in doubt from the section.

I perhaps grew overconfident in my remarks to pathologists, contending that the X-ray film was in a measure as important a method of determining pathologic conditions as was a microscopic section. The X-ray film is not as a rule understood by pathologists. They do not realize that it is an accurate

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chart of the relative atomic weights of all substances encountered by the rays on the way to the plate beneath the object shown. After all, a microscopic section is only an extremely thin slice of a part of the whole object. It varies with the direction in which the slice is taken, with the part that it is taken from, and with the artificial staining of the materials used to make it visible under the microscope. It is thus subject to much inaccuracy. From my point of view, the pathologist who neglects to study the X-ray film of a bone tumor is in much the same position as a röntgenologist who undertakes to contradict an opinion made from the microscopic slide. The film shows the manner in which the bone is eroded by the disease or enhanced by deposit of calcium. In a way it shows more than does a median section of the gross specimen.

I had been lecturing Doctor Ewing on this favorite theme (on which by the way he agreed) when the conversation turned to living pathology *versus* autopsy pathology. I argued that we surgeons saw many evidences of pathology in the living which the laboratory pathologist never saw. I instanced rupture of the supraspinatus tendon and Doctor Ewing admitted that he had never heard of it. I think the majority of other pathologists will admit the same. The subject of this paper is now introduced.

At the ordinary autopsy there is much to be done and much to be recorded and it is unusual for the joints to be opened and observations on their pathology added to those referring to the viscera. Still more unusual is it to open the bursa. Consequently, few pathologists ever open the subacromial bursa to study its pathology. This has been my hobby for thirty years. Whenever possible when attending an autopsy, I would ask for permission to open the subacromial bursa. I have also opened the bursa in many cases in the dissecting room at the Harvard Medical School, and I have had the opportunity to open it more than a hundred times in the living. In consequence of this experience, I have found that in elderly subjects (particularly in working people), the incidence of ruptured supraspinatus tendon is large. Unfortunately, I have not kept accurate account of the numbers of my observations, but I have always been able to find at least one instance of one of these ruptures in every set of twenty dissecting room subjects. I therefore formerly felt that the incidence in this class of material was surely over 5 per cent., but this work of Doctor Akerson's* has opened even my eyes.

The present study has been made from autopsy material obtained at a large municipal hospital (Long Island Hospital) for chronic conditions. The patients sent to this hospital are people who are aged and down-and-out, and owing to the chronic character of their diseases, cannot be cared for at the other Boston hospitals. Doctor Akerson has made a study from 100 specimens taken from fifty-two consecutive autopsies and the percentage of

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cases showing evidence that the supraspinatus tendon had been ruptured at some time during the lives of these patients is high—39 per cent. It may, therefore, be taken as a maximum and it may be expected that pathologists performing routine autopsies in general hospitals for acute diseases, where the ages average considerably younger, will find a decidedly smaller percentage. We have made no attempt to correlate the past histories of these patients as to trauma or occupation with the autopsy findings. It would have been hardly possible under the circumstances.

As a routine method of examination of these cases, we recommend the pathologist to employ the form of incision which we use in operations on the living. A cut is made on the anterior aspect of the shoulder-joint from the acromioclavicular articulation downward for about two inches. The fibres of the deltoid are separated and retracted and the roof of the bursa is incised between two pairs of forceps as one opens the peritonæum. When the lips of the wound are retracted, the whole inferior aspect of the bursa can be made to pass in review by rotating the humerus. The base of the normal bursa is smooth and spherical and almost as colorless as the cartilaginous surface of the head of the bone, though it lacks the bluish lustre of cartilage. Most rents in the tendons of the short rotators usually appear in this base as communications directly into the joint and are readily visible. Occasionally the tendon is ruptured beneath the base of the bursa, which is left intact. In the ordinary autopsy it would take but a few minutes' extra time to examine both bursæ. If lesions are found, the head of the bone with the insertions of the short rotators can be removed and studied. This was the method used by Doctor Akerson and his findings are good evidence that some sort of pathological process has been at work in the subacromial bursæ of these patients during their lifetime. One must understand that these findings are those accumulated by each individual subject in many years. They are end-results, not acute lesions. In asking Doctor Akerson to make this study, I have told him how important it is for surgeons to find out whether these lesions are usually of a traumatic nature, or whether a diseased or weakened condition of the tendon precedes the trauma and the rupture actually occurs through pathologic tissue.

There are four reasonable hypotheses to explain these lesions: (1) They may be the results of trauma (*i.e.*, rupture of tendon fibres, followed by imperfect repair). (2) The defects left as a result of the so-called "calcified deposits." (3) The result of necrosis of the tendon or other diffuse, pathologic process, or of the same phenomena which are known as arthritis in other joints. (4) The direct result of attrition (hypothesis of Meyer).

From the clinical and especially from the industrial point of view, it is very important that these questions should be answered. On the one hand, thousands of dollars paid annually by insurance companies, and, on the other hand, the question of utter poverty of many individuals, may depend upon this answer. My own experience has led me to the conviction that rupture of the supraspinatus tendon is by far the most common cause of industrial

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shoulder disability and that complete rupture is a more painful, more serious, and more disabling lesion than fracture of the humerus or dislocation of the shoulder. It is the usual cause of traumatic subacromial (subdeltoid) bursitis. I am at present writing a book to support this contention. Since I have been able clinically to diagnose cases of supraspinatus rupture with only a small percentage of error, and have in more than 40 cases sutured the ruptured tendon, my own conviction is naturally in favor of a traumatic cause. Yet I am by no means convinced that there is not an underlying degenerative process in the tendon which makes it prone to rupture. The frequency of finding that this is a bilateral condition, together with the fact that the lesion seldom occurs in young men, makes it highly probable that there is some general cause, which, with the trauma, produces the condition which we are studying.

I may not be correct in my contentions, but there is no doubt that Doctor Akerson has found defects in the supraspinatus tendon which might be explained as the results of traumatic rupture in thirty-nine out of 100 shoulder-joints taken from aged people of the laboring classes.

The object of this paper is to bring the attention of pathologists to a lesion which is of great importance in industrial surgery and which in the opinion of the writers, needs intensive study.

Doctor Akerson's Findings in 100 Shoulder Joints

Both shoulders examined.....	48
Single right shoulders.....	2
Single left shoulders.....	2
	100
Total autopsies	52
Males, 37; females, 15; total.....	52
Ages: 46-59	7 cases
60-79	35 "
80 and over	10 "
	Total
Right shoulders, 50; left shoulders, 50; total.....	100

Rupture of Supraspinatus Found

Right, 23 (46 per cent.); Left, 16 (32 per cent.); Average, 39 per cent.

Degree of Ruptures

Large enough to show the articular surface on opening bursa.....	21
Smaller than this but still quite apparent.....	18
Total	39

In thirty-nine cases the supraspinatus was ruptured either alone or in combination with adjoining tendons as follows:

With portion of subscapularis.....	6
With portion of infraspinatus.....	10
With infraspinatus and teres minor.....	2
With all other short rotators (in same patient).....	2

In only one case was a lesion found in other tendons (a small lesion in the infraspinatus) when the supraspinatus was intact.

The joint cartilage showed erosion in twenty-four cases in which the supraspinatus had been torn. No erosion was shown in any case in which the supraspinatus was not torn or when the tear was so small as not to expose the bone or cartilage when the bursa was opened. The amount of erosion was usually proportionate to the extent of damage in the tendon.

Condition of Biceps Tendon in 50 Cases

Exposed to view in gap.....	1
Could be pulled into gap.....	2
Evulsed from glenoid.....	6
Flattened	4
Frayed	5
Total	18

Bearing in mind that this series of lesions must represent the scars or attempts at repair of trauma or disease which had probably occurred many

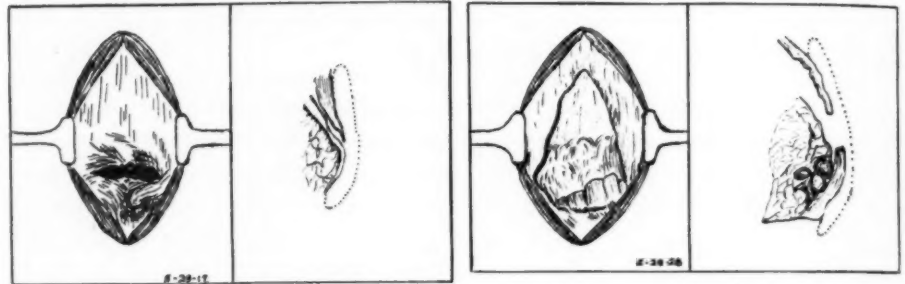


FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

FIG. 1.—A transverse tear of the tendon. At the base of the defect (shaded portion), is articular cartilage.

FIG. 2.—Vertical section near edge of same specimen as in Fig. 1. A falciform edge on the ruptured tendon and a rounding off of the tuberosity.

FIG. 3.—Here we see a triangular tear in the tendon. There are stubs of tendon on the tuberosity in a characteristic palisade-like formation.

FIG. 4.—A tag of tendon on the tuberosity. The tendon is retracted and thinner than the stub. In the tuberosity are small cyst-like cavities.

years previously, it seems fairly obvious that these defects in the tendon rarely, if ever, undergo complete repair. One may be reasonably sure from the series of lesions observed, as well as from findings at operations on the living within a few weeks or months after an injury, that the sequence of events is somewhat as follows:

1. A transverse rupture occurs across the breadth of the tendon near its insertion (Fig. 1).

2. Retraction of the muscle causes the rent to assume a triangular shape with its base on the tuberosity (Fig. 3).

3. A feeble effort at repair takes place, resulting in (a) rounding of the triangle by obliteration of the corners (in the horizontal plane) and (b) the formation of a falciform edge (in the vertical plane) of fibro-synovial tissue

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which smooths the edge of the rupture around the whole circumference (Figs. 5 and 8).

4. Gradual absorption of the tag of tendon which remains on the tuberosity (Figs. 7 and 8).

5. Recession of the now useless portion of the tuberosity to which the tendon was formerly attached (Fig. 8).

6. The formation of fibrocartilage on this surface to avoid friction as the tuberosity passes in and out under the acromion (Fig. 8).

Thus we may feel moderately sure that nature's method of repair is a palliative smoothing off of the rough edges rather than a restitution of substance. This must be true whether the cause of the defect is purely traumatic or the result of absorption from disease. This whole process takes many months or even years.

I have referred above to the question of interpretation of the findings in this series. There is little doubt that in a similar series of autopsies, the lesions above described will be found by any pathologist who cares to look

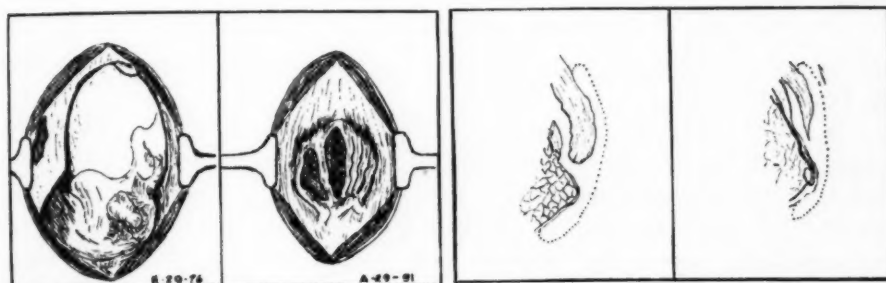


FIG. 5.

FIG. 6.

FIG. 7.

FIG. 8.

FIG. 5.—Extensive rupture involving supra- and infraspinatus. There is a smaller tear to the left. The wavy line represents the edge of the articular cartilage. There is new bone on the bare tuberosity.

FIG. 6.—Bands of tendon still crossing the defect. At the right are several slits in the tendon, i.e., the superficial laminae have torn away, but bands of the deeper portion of the tendon remain.

FIG. 7.—The tuberosity is receding and the edge of the tendon is rounded and blunt as compared to that in Fig. 8, which is more common and is falciform.

FIG. 8.—Shows a further rounding off of the tuberosity as compared to Fig. 7. Cartilage is forming over the exposed tuberosity.

for them. How will such lesions be interpreted in the future when they have been studied from the clinical and operative side as well as from the pathologic findings? We can touch briefly on some of the problems which have occurred to us.

In Favor of the Traumatic Origin.—(1) Foremost is the fact that there exists a clinical symptom-complex by which rupture of the supraspinatus can be diagnosed. The patient has a history of a considerable trauma; he can raise his arm only with great effort, if at all; there is lack of normal scapulo-humeral rhythm; there is a tender point corresponding to the facet of insertion of the supraspinatus where a slight sulcus and a slight eminence can be felt; there is a painful jog and characteristic crepitus as this tender point disappears beneath the acromion as the arm is elevated.

(2) The findings at operation are similar to those lesions which have

been found in this series at autopsy, although in the main those found at operation represent earlier stages of repair.

(3) Microscopic sections from cases in this series indicate loss of continuity of the fibres without serious signs of disease in the adjacent tendon.

(4) The supraspinatus tendon (perhaps owing to man's vertical position), is the locus minoris resistentii and is almost always involved. The rents in the other tendons extend laterally from that in the supraspinatus, even to the extent of evulsion of all of the tendons of the short rotators.

(5) The preponderance of right over left speaks for trauma.

Against a Traumatic Origin.—(1) Tissue removed from tendons of aged people and from cases operated on for lesions in this region, whether traumatic or not, show a necrosis which is a result of retrograde changes. This necrosis is similar in appearance in cases operated on for calcareous deposits. It is so common as to suggest it is a semi-normal senile change.

(2) The large number of bilateral cases (fourteen) found at autopsy, speaks against traumatism and in favor of some form of slow necrotic destruction.

(3) The general surgical profession has not recognized this lesion as a clinical entity which can be diagnosed and repaired by operation as claimed by Doctor Codman.

In Favor of These Lesions Being the Results of Calcified Deposits.—Since the X-ray was introduced, calcified deposits have been found many times in the supraspinatus tendon and in some of the other neighboring tendons. It is not uncommon for these deposits to be removed by surgery, but experience shows that all such deposits are absorbed sooner or later, even if not removed. That the lesions found in our series might in many cases be merely the defects left by previous calcified deposits must be admitted. Calcified deposits are often bilateral; so are these defects in the supraspinatus.

The exact method of formation of these deposits is not known. Sections from them indicate that where they exist, there is loss of continuity of the fibres of the tendon. It seems doubtful if, when they are absorbed, new tendon ever forms. It cannot be denied that the findings above described may in some cases be the defects left by these lesions, or we may assume that tendons weakened by such lesions in the past may tear readily.

In Favor of These Lesions Being the Result of Necrosis of Constitutional Origin.—This heading is inevitably associated with the question of arthritis. It includes it perhaps. The shoulder-joint (owing to its freedom in all directions, without close relations with other bones) is anatomically not likely to show the usual changes associated with arthritis. The joint is really made up of the short rotators, which, near their insertions, are blended with the capsule. Should we not expect therefore, that the arthritic changes common in other joints might appear in the shoulder-joint in the form of defects in the supraspinatus and other short rotators? One might open a subacromial bursa, see a defect in the supraspinatus with the asso-

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ciated atrophic and hypertrophic changes on the tuberosity and be satisfied with the diagnosis of arthritis. Space does not permit us here to enter into an extensive argument on the matter. Suffice it to say that we do not consider the changes found as comparable to such changes as are called arthritis in the hinge joints.

In Favor of the Theory That These Changes Might Be Caused by Friction.—We must refer to the writings of Dr. A. W. Meyer, Professor of Anatomy, Leland Stanford University, California. Doctor Meyer made an excellent case for the argument that laboring men using their shoulders to excess may actually, by friction between the humerus and the acromion, wear through the supraspinatus tendon and joint capsule, and even destroy the biceps tendon as it courses across the joint over the cartilaginous head of the bone.

From our understanding of accepted principles of pathology, such actual destruction by friction is well nigh impossible, but we grant that the same results may be brought about by persistent inflammation of these structures, caused by friction. Chronic inflammation in any structure tends to produce an initial hypertrophy followed by atrophy. We feel that it is conceivably possible that defects similar to those found in this investigation might come about from excessive overuse without a single serious trauma. We feel that such a consequence is unlikely and that in view of our clinical experience in which these lesions have been found within a few months after adequate injuries, the burden of proof is on those who feel that chronic overuse might produce extensive defects in the tendons inserted into the head of the humerus.

A purely anatomic argument against Doctor Meyer's theory is that the impingement of the head of the humerus on the lower surface of the acromion does not occur in the normal individual. The friction at this point is taken up by the outer side of the tuberosity which is covered with the lower surface of the bursa. Furthermore, the coraco-acromial ligament partially intervenes. The plane of the cartilaginous surface is distinctly below the plane of the tuberosity as the arm is abducted. As soon as the tendon is damaged, however, either by disease or trauma, there would be a marked jog in the motion at just the point at which the uppermost fibres of the normal tendon are inserted into the tuberosity. A trauma affecting these fibres would therefore start a vicious circle, changing the contour of the lower surface of the bursa so that there would always be a hitch at the point where this portion of the base passed beneath the acromion and coraco-acromial ligament. Chronic inflammatory changes would take place.

One is tempted to compromise by saying that many causes or combinations of causes may produce the same lesion; *i.e.*, a defect in the substance of the supraspinatus tendon.

e.g.: Constitutional conditions might produce changes similar to those produced in atheroma of the arteries. A trauma ordinarily easily withstood might rupture such a tendon.

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e.g.: A calcified deposit absorbed some years before might have destroyed enough tendon fibres so that a slight trauma later might rupture the remainder.

e.g.: A young man might rupture fibres which his active blood-supply would completely repair; one slightly older might fail in repair and have a calcified deposit form in a poor cicatrix; an elderly man might fail to repair such a rupture altogether, and show at autopsy the condition we find.

e.g.: Continued overuse might cause necrosis and atrophy. Laminated band after laminated band might break away from slight strains. A single severe trauma might complete the havoc.

Neither of us at present cares to take a very positive stand in explaining these findings. We are inclined to think that changes in the integrity of the tendon due to age, constitutional conditions or overuse are primary as a rule, but that trauma produces the actual rupture in most instances. The fact that these cases can be diagnosed clinically and the rupture sutured, influences our interpretation of the autopsy findings.

It is sometimes well to make comparisons. Consider the relative amount of pain and disability caused by bone sarcoma and by injuries to the supraspinatus. Unlike bone sarcoma, which is never diagnosed in an early stage and is seldom cured, rupture of the supraspinatus can be recognized early and promptly sutured. Contrast the literature of the two lesions. It would take hundreds of volumes to bind the literature of bone sarcoma, a dramatic, pathetic, rare condition, for which we can do next to nothing and which is of little industrial importance. On the other hand, the literature on rupture of the supraspinatus tendon, the most common cause of prolonged shoulder disability in industry, and a subject of great importance, has only just begun!

It seems as if hitherto pathologists had interested themselves only in diseases which may cause death. Modern industry now urges the pathologist to search for the causes of incapacity.

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* So far as I know there is at present no literature on the subject of this paper which deserves serious study, except that comprised in the above references. I have no doubt that Doctor Meyer and I refer to the same lesions which were studied by Doctor Akerson for this paper and can be found by anyone who wishes to look for them in similar material. Doctor Meyer's attention has been focused on the long head of the biceps; mine has been focused on the supraspinatus. Probably both of us are in a measure right, and in great measure wrong, but at least we have opened up the field for future students who wish to relieve persons incapacitated by lesions in this region of the body.

L'ÉPITHÉLIOMA ÉPIDERMOÏDE DU COL DE L'UTÉRUS A KÉRATINISATION PÉRILOBULAIRE

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LA VARIÉTÉ d'épithélioma sur laquelle nous attirons l'attention est caractérisée essentiellement par une anomalie histologique: les cellules, dont sont formés les cordons et les lobules du tissu néoplasique, au lieu d'évoluer et de se transformer en squames kératinisées de la périphérie au centre de ces cordons et lobules, comme on le constate habituellement, évoluent et se transforment du centre à la périphérie (ou bien simultanément dans les deux sens), de sorte que les cellules génératrices sont intérieures, au lieu d'être périphériques, et qu'il se forme une couche cornée au contact même du tissu conjonctif.

Cette anomalie, qui n'est pas très rare, est facile à constater. Néanmoins nous n'en avons trouvé aucune mention dans les ouvrages que nous avons consultés.

Voici la description complète, clinique, thérapeutique et histologique, d'un cas typique de cette variété.

CAS I (XIV—A, n° 614). Pl. . . ., cinquante-neuf ans.—Tumeur maligne du col utérin, degré II.

Histologie: épithélioma épidermoïde, kératinisation à la fois centro-lobulaire et péri-lobulaire.—Premier traitement curiethérapique, suivi d'hystérectomie. Récidive dans la cicatrice vaginale.—Deuxième traitement curiethérapique; survie actuellement de trois ans.* Début des symptômes en décembre 1925: leucorrhée, petites hémorragies à l'occasion des rapports sexuels. Hémorragie abondante au début d'avril 1926.

1926, 20 avril.—Premier examen à la Fondation Curie. Gros col utérin, dur, ulcéré au centre, lèvre antérieure fendue; cul-de-sac vaginal gauche rétréci et induré; utérus encore mobile; par le toucher rectal, on trouve un ganglion occupant la partie moyenne du paramètre gauche.—Degré II.

DU 22 AVRIL AU 5 MAI, PREMIER TRAITEMENT

Du 22 au 26 avril, *curiethérapie intérieure*: (a) sonde intra-utérine en caoutchouc, contenant trois tubes de radium bout-à-bout; teneur totale des tubes utérins 33,32 milligrammes de Ra-élément; filtration platine 1 millimètre; (b) dans le fond du vagin, trois tubes de radium, chacun dans un étui de liège (deux tubes maintenus par un colpostat dans les culs-de-sacs latéraux, un tube dans la concavité du ressort); teneur totale des tubes vaginaux 33,32 milligrammes de Ra-élément; filtration platine 1,5 millimètres. Dose utéro-vaginale totale 47,5 millicuries de radon détruit, par application continue, en quatre jours.

Du 27 avril au 5 mai, *curiethérapie extérieure*, limitée au côté gauche du bassin;

* Observation clinique et radiologique du Dr O. MONOD.

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trois champs d'irradiation, ayant chacun une surface de 150 centimètres carrés: un champ iliaque antérieur, un champ sacro-iliaque postérieur, un champ ilio-fémoral transversal; charge de radium quatre grammes; distance dix centimètres; filtration platine 1 millimètre. Dose 270 millicuries de radon détruit par champ en trente-quatre heures d'irradiation effective, échelonnées sur neuf jours. Ce traitement s'est effectué sans incident.

15 juin.—*Hystérectomie* abdominale totale exécutée, comme il était préalablement convenu, par le chirurgien de la patiente.

13 octobre.—Fond du vagin et paramètres indurés, sans ulcération, ni tumeur.

1927, 26 janvier.—Petite tumeur dure, d'environ 1 centimètre de diamètre, ulcérée, siégeant sur la cicatrice opératoire vaginale. *Biopsie*; l'examen histologique indique: *récidive*.

DU 7 AU 12 FÉVRIER, DEUXIÈME TRAITEMENT

Curiathérapie intérieure: dans le fond du vagin, deux d'abord, puis trois tubes de radium (même dispositif que pour le premier traitement); dose 27,8 millicuries de radon détruit, par application continue, en cinq jours. Aucun incident.

6 avril.—Disparition de la lésion. Cicatrisation. Induration du tissu conjonctif pelvien, sans tumeur. Aucun symptôme fonctionnel.

14 décembre.—Bon état général. Persistance de l'induration du tissu conjonctif pelvien. On soupçonne que le néoplasme fermé continue d'évoluer lentement.

1928, 4 juillet.—Exploration. Même état.

1929, 10 avril.—Exploration. Même état.

1930, 2 avril.—Exploration. Nodosités suspectes contre la paroi pelvienne, à gauche, perceptibles par le toucher rectal.

Trois ans se sont écoulés depuis le deuxième traitement, sans qu'une récidive apparaisse avec évidence.

Analyse Histologique du Cas I.—Il a été fait deux analyses histologiques: l'une de la tumeur primaire (prélèvement d'avril 1926), l'autre de la récidive (prélèvement de janvier 1927). La structure est la même. Il s'agit d'un épithélioma d'origine épidermique à évolution épidermoïde.*

Le point de départ de la tumeur paraît être dans le canal cervical; on trouve, en effet, un peu avant le point de transition entre l'épithélium pavimenteux et l'épithélium à cellules prismatiques, des signes indiscutables de transformation cancéreuse de l'épithélium pavimenteux, qui est soudé au tissu cordonal-lobulé de l'épithélioma.

Disposition architecturale.—Le tissu néoplasique est constitué par des cordons épais, renflés souvent en lobules. Ces cordons ne forment pas de réseau, et leur anastomose est rare. Les renflements lobulaires présentent fréquemment des incisures périphériques, et ils sont souvent au contact de cordons plus petits, ce qui témoigne de la formation de ramifications ou de bourgeons. Toutes ces formations ont des contours arrondis et parfaitement bien limités.

Le tissu conjonctif qui sépare les cordons ou lobules forme ordinairement de larges travées.

Structure du tissu néoplasique.—La partie reproductrice du tissu est une couche généralement épaisse de cellules qui n'ont pas de contours nets (protoplasma indivis). Les noyaux sont arrondis ou ovoïdes, quelquefois un peu bourgeonnants et incisés à leur

* Modifiant quelque peu la terminologie communément usitée en Amérique, et exposée par EWING (*Neoplastic Diseases*, 3^e édition, 1928), nous avons pris l'habitude depuis longtemps de distinguer les épithéliomas d'origine épidermique en deux groupes: les *épidermoïdes* dont les cellules se transforment finalement en squames, et les *non-épidermoïdes* dont les cellules ne se transforment pas en squames, les uns et les autres comportant plusieurs variétés.

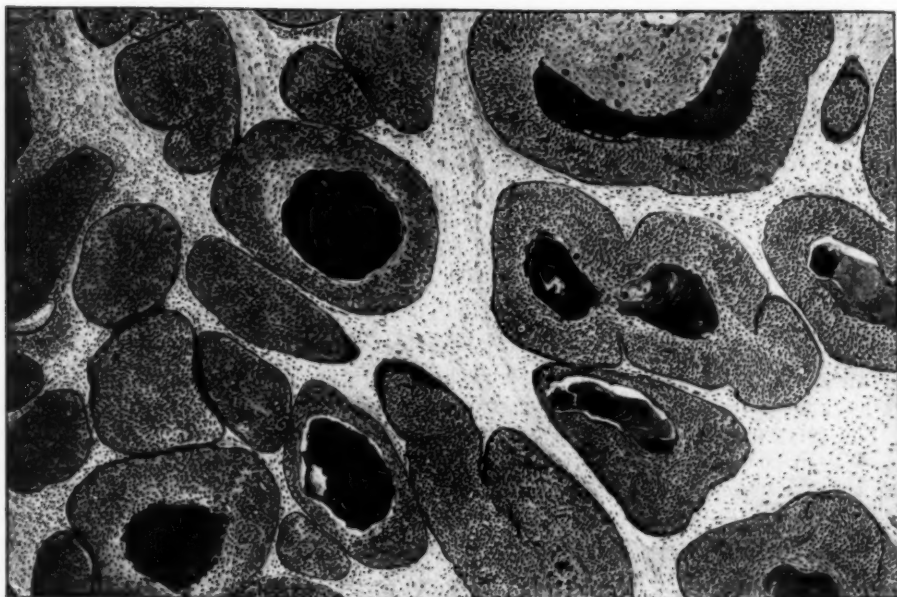


FIG. 1.—Cas Pl. . . , épithélioma épidermoïde du col de l'utérus, à kératinisation à la fois centro-lobulaire et péri-lobulaire. Fixation par un mélange de bichlorure mercurique, formaldéhyde et acide actéique; coloration par l'hémalum et l'éosine.—Grossissement du dessin: 85.

Remarquer: l'architecture cordonale-lobulée;—le stroma conjonctif, formé de travées larges, très pauvres en cellules migratrices; dans beaucoup de lobules et cordons, un amas intérieur (central ou excentrique) de cellules kératinisées; dans quelques uns, des cellules kératinisées isolément; tous les cordons et lobules sont limités, au contact du tissu conjonctif, par une mince couche, plus fortement colorée (couche cornée périphérique). Près du bord inférieur du dessin, coupe d'un tube glandulaire.

périphérie; dans les parties les plus jeunes du tissu, ils sont serrés les uns contre les autres; leur chromatine est formée de grains et de mottes généralement denses. Dans le



FIG. 2.—Même préparation.—Grossissement du dessin: 175. Un lobule de l'épithélioma.

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protoplasma on rencontre des fibres fortement colorables par l'éosine, isolées ou fasciculées, qui ont le même aspect que les fibres d'Herxheimer d'un épiderme normal. Ce tissu ressemble à une "couche génératrice d'épiderme," qui serait anormalement épaisse.

On rencontre de nombreuses karyokinèses, disséminées dans toute l'épaisseur du tissu germinatif. Les monstruosités nucléaires ne sont pas rares.

Evolution cornée.—Dans la partie centrale des cordons et lobules, il existe des cellules kératinisées, quelquefois isolées, le plus souvent agglomérées en amas plus ou moins volumineux. D'autre part tous les cordons ou lobules sont limités par rapport au tissu conjonctif par une couche mince et continue de cellules kératinisées. La kératinisation s'effectue donc dans deux sens opposés: en direction du centre ou mieux de l'axe des cordons, en direction de leur surface périphérique.

(a) Kératinisation centrale.—Elle n'existe que dans les plus gros cordons, renflés en lobules. L'amas axial ou central est formé de squames lamelleuses ayant conservé un noyau dense et homogène, ou de fragments de cellules sans noyau. Ces débris tantôt sont disposés sans ordre, tantôt montrent une disposition concentrique rappelant les globes cornés, tantôt semblent dissociés.

Entre le tissu actif et l'amas central kératinisé, tantôt il y a, tantôt il n'y a pas une couche de transition. La couche de transition est formée de grands corps cellulaires

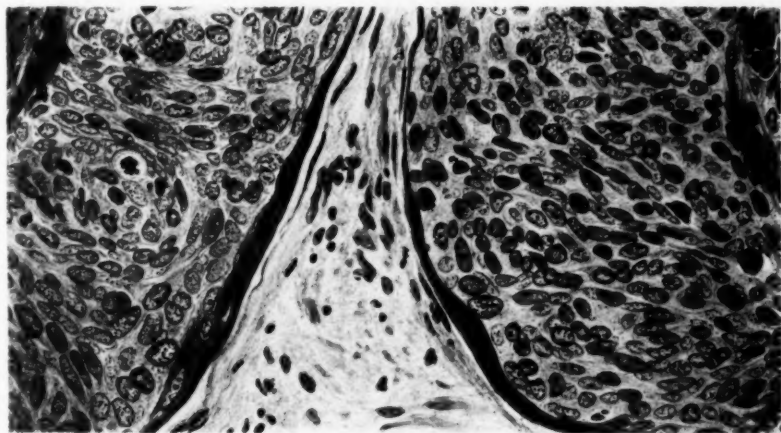


FIG. 3.—Même préparation.—Grossissement du dessin: 800.
Vue partielle de deux lobules contigus; tissu germinatif formé par une épaisse couche de cellules à limites indistinctes; pas de filaments unitifs du type Schultze-Ranvier, mais en quelques points une structure fibrillaire; kératinisation périphérique aboutissant à la formation de squames plates nucléées. Au centre des lobules, amas de squames cornées agglomérées; à la périphérie, les squames forment une couche mince composée de une à trois épaisseurs de cellules.

à contours assez distincts, possédant un noyau grand et vésiculeux; autour du noyau on voit quelquefois des corpuscules rappelant les gouttelettes d'éléidine de Ranvier, et assez souvent des faisceaux de fibrilles colorables par l'éosine. La couche de transition contient des cellules qui se kératinisent isolément.

Assez souvent l'amas kératinisé est excentrique, voisin de la périphérie du lobule ou même contigu au tissu conjonctif.

(b) Kératinisation périphérique.—Elle est constante. Tous les cordons, tous les lobules, sans exception, sont limités, contre le tissu conjonctif, par une mince couche continue de cellules lamelleuses, formant une ou deux assises, parfois trois. Ces cellules possèdent un noyau plat, formé de chromatine dense; leur protoplasma est fortement colorable par l'éosine. La couche kératinisée suit très exactement le contour du cordon; quand deux cordons sont contigus, leurs membranes kératinisées se juxtaposent.

A un faible grossissement, cette couche marginale apparaît comme une mince bordure

rose; et sa continuité porte de prime abord à interpréter cette bordure comme une vitrée conjonctive, interprétation qu'un examen plus attentif ne justifie pas: dans une préparation colorée par la méthode trichrome de P. Masson (hémalum—éosine—safran), les fibres conjonctives et les membranes vitrées sont, en effet, colorées en jaune.

Entre la zone reproductrice et la couche kératinisée périphérique, il existe souvent une ou deux rangées de cellules de transition, analogues à celles décrites autour de l'amas kératinisé intérieur.

La surface externe de la couche kératinisée est généralement lisse; parfois cependant

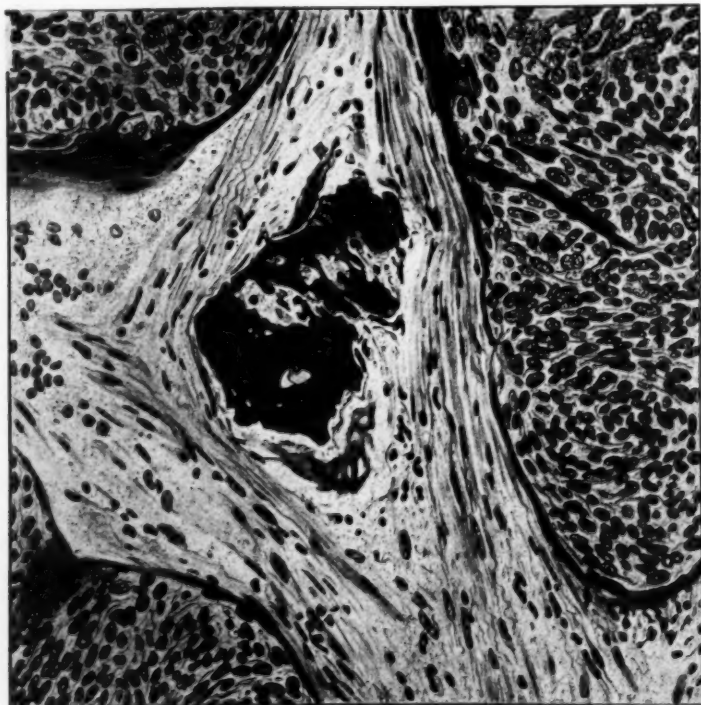


FIG. 4.—Même préparation.—Grossissement du dessin: 350.
Au centre du dessin, amas de débris cellulaires kératinisés (cordon spontanément stérilisé), que n'entoure aucune cellule néoplasique vivante.
En haut et à gauche la surface d'un lobule est vue obliquement, de sorte que les squames kératinisées se présentent à plat. Près du même point, du sang a fait irruption dans un espace (non pourvu d'endothélium, et par conséquent de nature non-vasculaire) interposé entre le tissu conjonctif et la surface du lobule.

quelque squame se soulève, comme pour se détacher. Fait remarquable, cette surface n'adhère absolument jamais au tissu conjonctif, comme c'est au contraire le cas au niveau des membranes basales ou vitrées. Souvent même, une rétraction s'est produite entre le tissu conjonctif et la surface du cordon ou lobule; et ces deux tissus sont séparés par une fente. Tantôt cette fente est vide; tantôt elle est remplie par du sang, dont on voit la fibrine coagulée et les globules. On pourrait se demander si le système cordonal lobulé, possédant un revêtement corné si spécial, ne se développe pas dans un réseau de vaisseaux lymphatiques. Mais les vaisseaux lymphatiques (qui ne subissent jamais d'accroissement dans un tissu envahi par une tumeur maligne) n'ont pas—à beaucoup près!—dans la région du col utérin un développement comparable à celui du système cordonal lobulé en question. D'ailleurs la fente péri-lobulaire se distingue parfaitement d'un vaisseau sanguin ou lymphatique, par l'absence d'endothélium.

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Il y a dans cet épithélioma, comme dans presque tous les épithéliomas épidermoïdes, une alternance très nette dans le développement des cordons. Les plus jeunes cordons (formés sans doute par des bourgeons appendus à des cordons ou lobules plus âgés) sont caractérisés par l'absence de kératinisation centrale, par les noyaux serrés et à structure dense de leur zone reproductrice. A un stade plus avancé, les cellules actives, quoique n'acquérant jamais des contours parfaitement distincts, s'agrandissent, se chargent de fibres colorables par l'éosine et leur noyau devient vésiculeux. Les cordons âgés possèdent un amas kératinisé intérieur gros, entouré d'une mince couche de tissu actif. Au dernier stade de leur évolution, les cordons ne sont plus représentés que par des résidus cornés, nus dans le tissu conjonctif, et s'y dissolvant sans intervention de leucocytes (Fig. 4).

Tissu conjonctif et leucocytes.—Les travées intercordinales sont formées de tissu conjonctif fibreux adulte. On y trouve des fibres collagènes, ordonnées en groupes parallèles, avec des fibroblastes typiques.

Il y a dans le tissu conjonctif intercordinal extrêmement peu de cellules mobiles: les polynucléaires sont complètement absents; les lymphocytes sont rares. On voit quelques petits groupes de plasmocytes. On ne trouve absolument aucun leucocyte dans les cordons et lobules, ni dans le tissu reproducteur, ni dans les amas kératinisés intra-lobulaires. Et ce caractère négatif contraste remarquablement avec l'abondance ordinaire d'une population leucocytaire variée dans les épithéliomas épidermoïdes habituels.

Dans la muqueuse du canal cervical (sur l'un des bords de la préparation histologique), la proportion des leucocytes et des plasmocytes, et la diapédèse des polynucléaires à travers les parties non cancérisées de l'épithélium pavimenteux stratifié sont, au contraire, normales.

Les vaisseaux sanguins sont représentés par des artérioles et des capillaires, dont beaucoup ont en coupe transversale une forme irrégulière et sont d'un calibre plus grand que celui de capillaires normaux. Ces vaisseaux se trouvent exclusivement dans le tissu conjonctif: on ne voit pénétrer dans les cordons et lobules épithéliomateux aucun bourgeon vasculo-conjonctif.

On rencontre quelques tubes glandulaires, qui ont la structure des glandes du col utérin. Il n'existe pas de signes de substitution du tissu épidermique cancérisé au tissu glandulaire.

Nous n'avons jusqu'à présent étudié, pour y rechercher cette anomalie histologique, que soixante-quinze épithéliomas pavimenteux du col de l'utérus, pris au hasard parmi un millier (environ) de cas traités à la Fondation Curie de 1919 à 1929 inclus. Sur les soixante-quinze cas examinés, nous avons trouvé six fois l'anomalie en question (soit 8 pour cent).

Voici de courts résumés des observations cliniques et radiologiques des cinq autres cas.

CAS II (XIV—A, n° 486).* Si . . . , quarante ans.—Hystérectomie supra-cervicale pour fibromyome en 1922.—En janvier 1925: tumeur ulcérée occupant le col, les culs-de-sacs vaginaux antérieur et gauche; invasion bilatérale du paramètre; utérus bloqué; infiltration de la cloison vésico-vaginale, avec ulcération de la vessie.—Degré IV.

Histologie: épithélioma épidermoïde, disposition cordonale-lobulée; évolution cornée péri-lobulaire.

Röntgenthérapie du 13 janvier au 10 mars 1925.

Décès 27 octobre (survie sept mois et demi).

CAS III (XIV—A, n° 496).* Bor . . . , quarante-deux ans. En février 1925 grosse

* Observations clinique et radiologique du Dr H. COUTARD.

tumeur du col utérin, remplissant le vagin, ulcération des culs-de-sacs antérieur et droit; tumeur du paramètre droit, induration du paramètre gauche; utérus bloqué.—Degré III.

Histologie: épithélioma épidermoïde, disposition architecturale variable; évolution cornée ordinairement centrifuge, au contact du tissu conjonctif.

Röntgenthérapie du 19 février au 5 mars 1925, abandonnée en raison du mauvais état général.

Décès le 2 juin (survie trois mois).

CAS IV (XIV—A, n° 560).† Au . . . , quarante-huit ans.—Hystérectomie pour tumeur maligne du col le 10 août 1923. En novembre 1925: ulcération avec induration étendue du fond du vagin; signes d'envahissement de la vessie; bloc néoplasique unissant le fond du vagin à la paroi pelvienne des deux côtés.—Degré IV.

Histologie: épithélioma épidermoïde, disposition cordonale-lobulée; évolution cornée presque partout péri-lobulaire.

Curiethérapie du 5 au 11 novembre 1925; irradiation seulement extérieure, bientôt interrompue par le mauvais état général et la fièvre.

Décès le 15 octobre 1926 (survie onze mois).

CAS V (XIV—A, n° 738)*. Mar . . . , cinquante-trois ans.—Hystérectomie supracervicale pour fibromyome en 1925. Ulcération du col, sans induration des culs-de-sacs, ni du tissu conjonctif pelvien.

Histologie: épithélioma épidermoïde, disposition cordonale-réticulée. Evolution cornée péricordonale.

Premier traitement, curiethérapie vaginale du 23 au 28 juin 1927.

Récidive locale constatée le 17 avril 1929.

Deuxième traitement, curiethérapie vaginale du 14 au 19 mai 1929, puis *röntgenthérapie* du 24 mai au 8 juin 1929.

Guérison douteuse (janvier 1930).

CAS VI.‡ Luc . . . , soixante ans.—Induration générale du fond du vagin; tumeur de l'isthme utérin; induration du paramètre gauche, avec rétraction de l'utérus de ce côté.—Degré II.

Histologie: épithélioma épidermique, à évolution épidermoïde seulement ébauchée; disposition cordonale-lobulée; lyse centro-cordonale avec formation de cavités intra-épithéliales; kératinisation péri-lobulaire fréquente avec formation de squames au contact du tissu conjonctif.

Traitement radiothérapique combiné par curiethérapie intérieure et par rayons X, du 2 avril au 1er mai 1929.

La symptomatologie des six cas que nous avons observés ne présente aucun caractère spécial. Le nombre des cas étudiés est trop petit, et ces cas présentaient des degrés d'extension trop inégaux, pour qu'il soit possible de se faire une opinion sur la radiosensibilité de cette variété, comparative-ment à d'autres.

L'intérêt de cette variété d'épithélioma du col utérin est donc confiné actuellement à l'histologie pathologique. A cet égard, les faits principaux se résument ainsi:

(1) Dans les six cas étudiés, les situations relatives de la couche germinale ou reproductrice du tissu épithéliomateux et de sa couche stérile sont inversées

† Observation clinique et radiologique du Dr O. MONOD.

* Observation clinique et radiologique des Drs G. RICHARD et J. PIERQUIN.

‡ Observation clinique et radiologique du Dr G. RICHARD.

par rapport à l'état de choses habituel. La couche germinale, au lieu d'être en contact avec le tissu conjonctif et à proximité du réseau capillaire sanguin, est séparée du milieu nourricier par la couche stérile des cellules en voie de kératinisation, ou déjà transformées en squames cornées. Quelquefois (dans deux de nos six cas), l'évolution cornée se fait à la fois vers la périphérie et vers le centre des cordons. Nous avons recherché soigneusement la pénétration possible de vaisseaux capillaires dans les cordons: nous ne l'avons jamais constatée. Par conséquent nous devons admettre que, dans cette variété d'épithélioma, la nutrition du tissu néoplasique s'effectue par diffusion du plasma à travers la couche stérile, en sens inverse des conditions habituelles.

Cette inversion du sens habituel de la transformation des cellules épidermiques et du courant nourricier qui alimente leur couche germinale n'est pas, dans nos observations, un phénomène accidentel n'intéressant que de petits territoires d'un lobule épithéliomateux. C'est un phénomène régulier; il intéresse la plus grande partie du tissu néoplasique, et il peut se généraliser à toute l'étendue du système cordonal-lobulé qui constitue ce tissu. On le retrouve sous modification dans toutes les parties du tissu de la récidue (cas I, rapporté en détail). Nous devons conclure de cela que, dans un épiderme, la transformation des cellules aboutissant à la formation de squames stériles ne résulte pas du fait que les couches successives de cellules s'éloignent de plus en plus du milieu nourricier. Nous montrons, en effet, que cette transformation n'est pas empêchée lorsque les cellules les plus anciennes sont en contact avec le tissu conjonctif. L'évolution cornée des cellules épidermiques paraît être la manifestation d'une propriété inhérente à ces cellules.

(2) L'interposition anormale d'une couche continue de squames cornées entre le milieu vasculo-conjonctif et le tissu fertile de l'épithélioma épidermoïde semble empêcher la pénétration des leucocytes dans le tissu épithéliomateux.

Il y a des cas, il est vrai, où la population leucocytaire de la tumeur est extrêmement clairsemée, le tissu conjonctif intercordonal étant presque désert (exemple: cas I décrit en détail). Mais dans d'autres cas, au contraire, les espaces conjonctifs sont abondamment peuplés de lymphocytes et de plasmocytes. Toujours les leucocytes ont été trouvés en nombre extrêmement minime dans les cordons épithéliomateux, ou même ils en étaient tout à fait absents. Jamais il n'a été trouvé d'amas de leucocytes au contact de la couche cornée qui revêt la périphérie des lobules. Cela porte à penser d'une manière générale, que les leucocytes ne jouent pas un rôle indispensable dans la transformation cornée des cellules épidermiques.

(3) Dans la plupart des variétés histologiques des épithéliomas épidermoïdes, on peut constater une alternance de stades entre les diverses parties du système cordonal-lobulé qui les constituent. Les cellules germinales à corps protoplasmique encore incomplètement individualisé, les cellules polyédriques, les cellules à éléidine (quand elles existent), les cellules en

cours de kératinisation, les squames ayant achevé leur évolution ne se succèdent presque jamais régulièrement en tous les points du système cordonal-lobulé: la composition cellulaire est alternante d'un point à un autre. Dans la variété que nous avons décrite, cette alternance est nette. Le stade le plus jeune est représenté dans le système cordonal-lobulé par des régions intérieures, dont la structure est syncytiale, et où les noyaux sont petits, serrés les uns contre les autres et riches en chromatine. Le stade ultime est représenté par des amas de squames (cas I), ou bien par des squames isolées les unes des autres (cas III) dans le tissu conjonctif.

RÉSUMÉ

Nous décrivons dans cet article les particularités histologiques d'une variété d'épithélioma du col de l'utérus, que nous dénommons: épithélioma pavimenteux stratifié, à évolution épidermoïde, à transformation cornée péricordonale. Cette variété a été rencontrée dans 8 pour cent des cas d'épithélioma pavimenteux stratifié du col. Elle ne paraît pas présenter de caractères particuliers dans son évolution clinique. On ne peut encore rien dire de sa radiosensibilité.

IV

RADIUM AND RÖNTGEN RAY THERAPY

- W. S. LAZARUS-BARLOW, M.D., F.R.C.P. West Mersea, Essex, England
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"The Experimental Use of a Large Quantity of Radium in Treatment."
- DOUGLAS QUICK, M.D. New York, N. Y.
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"Interstitial Radiation in Metastatic Cervical Nodes of Epidermoid Carcinoma."
- LLOYD F. CRAVER, M.D. New York, N. Y.
Attending Physician, Memorial Hospital.
"A Case of Malignant Thymic Tumor, Probably Carcinoma, Treated by Heavy Irradiation; With a Report of Autopsy Findings."
- RALPH E. HERENDEN, M.D. New York, N. Y.
Röntgenologist to the Memorial Hospital.
"The Röntgen-ray Treatment of Giant Cell Tumors of Bone."
- GEORGE E. PFAHLER, M.D. Philadelphia, Pa.
Professor of Radiology, University of Pennsylvania.
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- HERMAN WINTZ, M.D., PH.D. Erlangen, Germany
Director of the Woman's Clinic, University of Erlangen.
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- CURTIS F. BURNAM, M.D. Baltimore, Md.
Associate Professor of Gynecology, Johns Hopkins Hospital.
"The Treatment of Cancer of the Body of the Uterus by Radiation."
- JAMES HEYMAN, M.D. Stockholm, Sweden
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- WILLIAM P. HEALY, M.D. New York, N. Y.
Attending Gynecologist, Memorial Hospital.
"The Treatment of Carcinoma of the Cervix Uterus."
- ANTOINE LACASSAGNE, M.D. Paris, France
Associate Director of the Radium Institute of the University of Paris.
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- J. E. GENDREAU, M.D. Montreal, Canada
Director of the Radium Institute of Montreal.
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THE EXPERIMENTAL USE OF A LARGE QUANTITY OF RADIUM IN TREATMENT

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THE idea that if a given agent be beneficial in small quantities it will be more beneficial in large is ingrained in human nature. Hence it was only reasonable to expect an attempt to utilize large quantities of radium in the treatment of cancer, soon after it became evident that the small quantities hitherto available afforded results that were beneficial to an astounding extent. Between August, 1919, and August, 1920, such an attempt was made at the Middlesex Hospital, London, with a quantity of hydrated radium bromide amounting to nearly five grams (representing about two and a half grams of the element) that was lent to the hospital by the Medical Research Council. In due course an account of the various investigations conducted was published under the title of "The Medical Uses of Radium" (Medical Research Council, Special Report, Series No. 62, 1922).

On some of the more definitely histological investigations the report was extensive, but the results of the therapeutic inquiry did not seem to call for description in detail. Since, however, treatment with large quantities of radium, later, was examined in the Radium Institute, Paris, and is now being conducted at the Westminster Hospital with four grams of radium element lent for the purpose by the National Radium Commission of Great Britain it seems that a detailed account of a somewhat similar experiment carried out ten years ago would be of use to those now engaged in the work.

The inquiry at the Middlesex Hospital was in the nature of team-work. The patients were under the care of the physicians and surgeons of the hospital; the physical determinations were carried out by Professor Sidney Russ; the blood examinations and some of the clinical observations were made by Dr. Helen Chambers; and, in the main, I was responsible for the actual treatment and the clinical notes. For the present paper and for any opinions advanced therein I am alone responsible. Although I have now retired, they are based upon the detailed records made at the time of the experiment, to which I have access by the kindness of the authorities of the Middlesex Hospital.

The physical material.—Considerations of technic and the experimental basis for therapeutic work are considered in some detail in the Medical Council's Report to which reference has been made. Here it will suffice to say (1) that gamma radiation was used; (2) that the radium was contained in a circular brass box 11.7 centimetres in diameter; (3) that the radium box was placed as close as possible to the part to be irradiated short of actual

contact; (4) that an exposure of approximately eight hours under the conditions in (3) was necessary to prevent Jensen rat sarcoma cells from growing when subsequently inoculated into normal animals; (5) that a continuous irradiation of four to five hours was regarded as the limit which the human skin would tolerate; (6) that such an exposure was unlikely to be lethal to the cancer cells, particularly at a depth, and (7) that the production of a radium burn was of inferior importance to the attempt at influencing the disease beneficially.

The duration of exposure.—Of the 108 cases considered here, seventy-seven received a single exposure that lasted as a rule four hours if only one site was irradiated or five or six hours if more than one region (*e.g.*, front and back, both sides of thorax) was treated. An exposure was divided into two or three portions in order to allow intervals for food and rest. Twenty cases received two exposures at an interval of a fortnight upwards according to circumstances, the total duration of exposure being generally between eight and eleven hours. In six cases the patient received three exposures at intervals but the total duration of exposure was again generally eight to eleven hours. In four cases the patient received four exposures at intervals and the total duration of exposure varied greatly, being eight, twelve, sixteen and twenty-one hours, respectively. In one case (lymphosarcoma of thorax and neck) the patient received six exposures, lasting in all twenty-three hours. In most cases of repeated exposure a second or subsequent exposure was given because the improvement noted after the first exposure was not maintained. In a few, the exposures were given with an interval of less than a fortnight in the hope of producing a lethal effect on the neoplastic cells by summation of irradiation. In all such cases, however, one was handicapped by the great probability of producing a severe radium burn.

The clinical material.—Inasmuch as it seems desirable for our present purpose that the amount of radium under consideration should be constant and as some of the radium was removed from the brass container from time to time at a later date in order to prepare tubes containing small quantities and radium needles, the number of cases analyzed here is less than that contained in the Medical Research Council Report (*i.e.*, 168). In the present paper 108 cases are included; in some, the information is meager but all cases treated during the period are presented without omission. With few exceptions the treatment was undertaken for malignant disease and usually the disease was in a very advanced stage; in such an experiment it was felt that it was only justifiable when no other recognized form of treatment was possible.

On examination the results in the present smaller number of cases agree in the main with those contained in the list given in the Medical Research Council Report. The only difference of importance arises in connection with cases of cancer affecting the breast. Thus a discrepancy occurs between the present and the Medical Research Council Report in respect to the ultimate results of cases, due in large part to information received subsequent

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to the publication of that report. In the present series of thirty-seven breast cases it is known that at least twenty-eight deaths occurred (*i.e.*, 76 per cent.), whereas the number of deaths in the entire series of seventy-eight breast cases contained in Table II of the Medical Research Council Report is only twenty-four (*i.e.*, 31 per cent.). The fact supports once more the contention that early reports of results in cases of cancer are dangerous particularly when cancer of the breast is under consideration.

For our present purpose the cases at our disposal are grouped in three ways: (A) The whole series of 108 cases is considered in respect of certain immediate or early constitutional and local effects. (B) The 108 cases are subdivided into seven classes, *viz.*, breast, thirty-seven cases; tongue, and mouth, including neck to oesophagus, twenty-six cases; rectum, six cases; skin including lip, seven cases; malignant disease at sites not included above, twenty cases; lymphadenoma, lymphosarcoma and leukaemia, nine cases; other conditions, three cases. (C) A comparison is made between growths that were certainly or probably sarcomatous, twenty-six cases, and growths that were certainly or probably carcinomatous, seventy-three cases.

(A) *Immediate or early constitutional and local effects. The blood.*—It was thought that blood examination might afford some indication of the radium action and in forty-two cases examinations were made before irradiation and as far as possible on the second and seventh days after irradiation. The actual findings are given in the Medical Research Council Report; here they are summarized and the means alone are given below:

Means of All Cases of Blood Examination
Males, 22 Cases

	Hæmo- globin	Hæmo- globin index	Red blood-cells	White blood-cells	Neutro- philes per cent.	Lymph- ocytes per cent.	Large mono- nuclears per cent.
Before radiation.....	88.8	89.3	4,973,000	18,400	72.1	23.3	3.1
Two days after radiation.....	87.5	88.6	4,935,000	16,650	75.0	20.1	3.9
Seven days after radiation.....	87.3	85.7	5,094,000	15,000	69.8	24.3	5.0

Females, 20 Cases

	Hæmo- globin	Hæmo- globin index	Red blood-cells	White blood-cells	Neutro- philes per cent.	Lymph- ocytes per cent.	Large mono- nuclears per cent.
Before radiation.....	86.8	81.2	5,348,000	13,200	67.0	27.6	4.4
Two days after radiation.....	81.4	77.9	5,228,000	12,770	72.9	22.4	3.7
Seven days after radiation.....	80.1	76.9	5,207,000	11,400	71.0	22.1	6.0

That the foregoing represents the facts with fair accuracy is shown by the means afforded by twenty-six cases (fourteen males, twelve females) in each of which the entire series of three observations was available.

From these observations we may conclude that exposure to the gamma rays of a large quantity of radium causes a diminution in the numbers of erythrocytes and leucocytes from the first; that the hæmoglobin and

	Hæmo- globin	Hæmo- globin index	Red blood-cells	White blood-cells	Neutro- philes per cent.	Lymph- ocytes per cent.	Large mono- nuclears per cent.
Before radiation.....	85.9	83.3	5,154,000	17,150	73.2	24.0	2.9
Two days after radiation.....	85.9	83.9	5,115,000	15,740	74.9	20.2	3.9
Seven days after radiation....	82.8	81.3	5,092,000	14,230	69.4	23.9	5.8

hæmoglobin index undergo a progressive decline during the week after exposure; and that there occurs an alteration in the relative percentages of neutrophile cells, lymphocytes and large mononuclear cells indicating an early destruction of lymphocytes and a progressive increase in the number of large mononuclear cells. These results are in accord with observations made on the blood in experimental animals and determined histologically (see Medical Research Council Report, pp. 46, 58, 85, 98, 108, 113).

Vomiting and nausea.—In eight cases vomiting was noted during or shortly after the radium exposure and in a few other cases there was some degree of nausea without vomiting. The vomiting was often severe and lasted for several days. It seemed to be dependent upon radiation effects upon the stomach itself for in all but one case (perineal irradiation) the stomach must have received an appreciable amount of gamma radiation from its proximity to the primary region of treatment. It must be conceded, however, that in many other cases in which the conditions of radiation were apparently identical, no vomiting or nausea occurred.

Erythema and dermatitis.—Thirty-nine cases showed a greater or less degree of skin implication by the radium rays. Eighteen cases developed a severe radium burn of the usual character and owing to the large area of irradiation such a burn was often nearly as large as the palm of the hand, deep, persistent and showing little inclination to heal. In thirteen additional cases there was a severe but more superficial dermatitis and in eight more there was erythema which ended in bronzing of the skin. The effects seemed to be due to the gamma radiation, for in one case in which half the area to be irradiated was covered with a sufficiency of oiled silk to exclude secondary beta rays, no difference was observed in the subsequent dermatitis over the protected and unprotected areas.

Other local results.—Local œdema occurred in five cases and was spread over a far greater area than the diameter of the radium capsule. A spreading septic cellulitis which started in the irradiated area and was rapidly fatal occurred in two cases. Local hæmorrhage occurred in four cases. Degenerative changes leading to softening and evacuation of pus-like material from a hitherto solid mass occurred in five cases and increase in the area of ulceration in six cases; an enhancement of the foul condition of the mouth was noted in four cases of cancer affecting this part and probably is of the same character. In nine cases the local pain was diminished; in eight it was increased.

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The region of disease.—In forty-four cases there was an early improvement in the irradiated region of disease as determined by inspection aided often by periodic measurements and photographs. Sometimes this improvement was remarkable and in eleven cases which had been deemed inoperable before exposure to radium the subsequent condition was such that surgical removal of the mass was undertaken (breast, seven; supraclavicular glands, one; sarcoma of tibia, one; sarcoma of thigh, one; carcinoma of calf, one. But with very few exceptions such improvement was of short duration; occasionally a second, or even a third irradiation was followed by a certain amount of improvement, but as a rule rapid extension occurred until death. Even of the eleven cases mentioned above as having undergone surgical removal of the mass, the final results dated from the first radium exposure were as follows. Breast cases: death occurred in five cases in nine and a half, fifteen, fifteen, seventeen and twenty-three months respectively, and two cases were lost sight of in good health after eight and sixteen months respectively. The sarcoma of tibia case died ten months and that of sarcoma of thigh thirty months after the first exposure to radium while the carcinoma of calf case was alive and well four years after the first irradiation and that of cancerous supraclavicular glands was alive and well six and a quarter years after the first irradiation. Of the remaining thirty-three cases in which local improvement was recorded after the initial irradiation, twenty-two died and six were lost sight of within twelve months of the first radium treatment, two died within eighteen months, two breast cases and a case of chronic adenitis of the neck were alive and well when lost sight of respectively seventy-five, seventy-six and forty-five months after the first radium treatment.

(B) Cases considered according to the site of the disease. Breast (thirty-seven cases, all malignant).—Of the thirty-seven cases, twenty-seven, or 73 per cent., either died in hospital or returned to their homes to die. The period intervening between the first exposure to the large quantity of radium varied between a few days and three years; in ten cases it was nothing to six months, in eleven cases seven to twelve months, in three cases twelve to eighteen months and in the three remaining cases death occurred at twenty-three, thirty-five and thirty-six months, respectively. The first irradiation was separated from death by a mean period of ten months; in this connection it may be remembered that the mean duration of untreated cancer of the breast from the reputed date of onset to death is approximately thirty-nine months. Concerning the remaining ten cases that were lost sight of short notes are given below.

- (1) Amputation after irradiation: lost sight of eight months after one exposure of four and three-quarter hours. Last note: "Recurrences in skin and axilla."
- (2) Recurrence in skin, axilla, supra- and infraclavicular spaces: lost sight of nine months after the first of two exposures totalling seven and a half hours. Last note: "Extension of disease but health fair."

- (3) A single recurrence in skin after operation: lost sight of ten months after one exposure of three hours. Last note: "No sign of nodule, feels well."
- (4) Recurrence seven years after operation: lost sight of twelve months after one exposure lasting five hours. Last note: "In fair general health."
- (5) Breast, axilla, sternum: lost sight of fifteen months after one exposure of four hours. Last note: "Breast growth quiescent."
- (6) Breast, axillary and supraclavicular glands, eight years' duration: lost sight of sixteen months after two exposures, totalling eight and a half hours. Last note: "Growth quiescent, no supraclavicular growth, doing her work."
- (7) Duct carcinoma (operable), amputation six weeks after one exposure lasting five hours: lost sight of four years after radium exposure. Last note: "In good health."
- (8) Breast (operable), amputation one month after one exposure lasting three and three-quarters hours: lost sight of four and a quarter years after radium exposure. Last note: "Apparently well."
- (9) Recurrences (seven years after operation) in supra- and infraclavicular spaces: lost sight of six and a quarter years after one exposure lasting five and a half hours. Last note: "No signs of recurrence."
- (10) Recurrence in supraclavicular space: lost sight of six years and four months after the first of two exposures totalling nine and a half hours. Last note: "No recurrence detected; in good health."

Of these cases Nos. 7, 8, 9 and 10, I think, may fairly be claimed as satisfactory though how far the result is to be ascribed to action of the radium cannot be determined.

One case in the group which terminated fatally is of peculiar interest in the present connection. Prior to the final admission to hospital the patient had suffered from a cancerous ulcer of one breast which healed completely under X-ray treatment; on admission she had a similar ulcer in the other breast and this under three exposures to the large quantity of radium totalling twelve hours improved very considerably, cicatrization taking place around the edges. Later the ulcer became indolent and finally the growth extended. She died eighteen months after the first exposure. The beneficial effect of X-rays and later of gamma rays upon two separate cancer masses raises the question whether a constitutional condition existed in this patient which enabled her to react to irradiation in an unusually favorable manner. It is undoubted that of two cases apparently similar the one may react well, the other badly, to the same degree of irradiation, so that the existence of a constitutional factor in determining the result seems to be possible.

Tongue and mouth, neck, œsophagus (twenty-six cases, all malignant).— Of the twenty-six cases all but one are known to have died from their disease. The mean duration of life in the twenty-five cases that died was

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3.7 months from the first exposure to radium. In seven of the cases there was a temporary local improvement, in six there was no recognizable change, in eleven a definite change for the worse was recorded. The surviving case was that of a man who received one exposure of two hours before partial removal of tongue and glands and seventy days later an exposure of two and a quarter hours. He was lost sight of four years and seven months after the first exposure; last note: "No recurrence, fairly well."

Rectum (six cases, all malignant).—Death occurred in all, on an average of 5.6 months after the first exposure to radium. Three of the cases developed severe radium burns over the sacrum. Relief of pain was recorded in three cases but otherwise no benefit was discernible.

Skin including lip (seven cases, all malignant).—Six cases died on an average of six and a quarter months after the first exposure to radium; two of these showed a temporary improvement. The seventh case was that of a man with a large fungating carcinoma of the calf. He was lost sight of four years after one exposure of five hours which was followed by so great a diminution of the growth that it was removed surgically a month later.

Malignant disease at sites other than those mentioned above (twenty cases).—The sites of disease were parotid, four; cervix uteri, two; colon, two; bone, four; abdomen, chest, prostate, testicle, bladder, stomach, thigh, lung, one each. Of the twenty cases seventeen are known to have died and with the exception of two cases to which reference is made below the mean duration of life after the first exposure was 3.4 months. One case was lost sight of nine months after the first exposure: "worse," one after twelve months: "condition unchanged," and in one the result was entirely doubtful owing to absence of record. Four cases showed a temporary diminution in size of the growth or other improvement but in the remainder there was nothing noteworthy. Two cases that ended fatally were remarkable for their length of survival, the first being that of a man with sarcoma of testicle who lived three years and two months after one exposure of four and a half hours to the large quantity of radium, the other being that of a man with a large sarcoma of thigh who lived two and a half years after four hours' irradiation and subsequent surgical removal of the mass.

Lymphadenoma, lymphosarcoma, leukæmic conditions (nine cases).—In all the cases in this group there was enlargement of lymphatic glands or spleen or both. In one case the result is entirely doubtful owing to lack of record. The remaining eight cases died, respectively, three days, ten days, fourteen days, four months, four and a half months, seven months, nineteen months and forty-two months after the first exposure to the large quantity of radium. Two cases are worthy of further remark.

CASE I.—A medical man admitted apparently moribund with pronounced lymphosarcoma of neck and thorax. The first exposure, lasting three hours, was followed by so great a relief that further exposures of three and a half hours, two and a half hours and three hours were given over various sites of neck and thorax during the next three days. Sixteen days after admission he left London for his home in Northern Ireland

in a very fair condition but two months later, the condition having reverted, he returned to London for further radium treatment with the large quantity. Two exposures of five and six hours respectively were given within twelve days and again the improvement was remarkable. Once more he returned home but the condition rapidly became worse and he died four months after the first exposure to radium.

CASE II.—Lymphatic leukaemia with enlarged spleen and glands in both groins. In this case the changes produced in the numbers of red and of white blood-cells by a single exposure lasting five hours over the splenic area were determined daily at 5 P.M. by the same skilled observer using the same instruments. They were as follows:

	Before irradiation	Immediately after irradiation	Day 1	Day 2	Day 3	Day 4	Day 5	Day 7
Erythrocytes.....	3,040,000	1,831,000	1,508,645	1,415,625	1,716,250	1,956,250	1,884,375	2,262,500
Leucocytes.....	326,708	219,687	67,937	98,437	35,000	36,250	52,187	59,375
Neutrophiles per cent.....	—	1	1.5	—	—	—	1	1
Lymphocytes per cent.....	55	96	92	73.5	63	92	11	95
Large mononuclears per cent.....	45	3	6.5	26.5	37	8	88	4

On the fourth, fifth and seventh days, it was uncertain whether cells should be classed as lymphocytes or large mononuclear cells; they were smaller than large mononuclears in earlier specimens but definitely larger and less deeply stained than lymphocytes.

Other conditions (three cases).—Of these cases one with chronic adenitis of neck was lost sight of apparently quite well three years and nine months after one exposure lasting five and a quarter hours; one with keloid over the site of a former mastoid operation was lost sight of, unimproved, thirteen months after one exposure lasting three hours, and one suffering from a sub-sternal mass of doubtful nature was lost sight of in a worse condition eighteen months after the first of three exposures, lasting in all ten and a quarter hours.

(C) *Comparison between sarcomatous and carcinomatous cases.*—For this comparison there are available twenty-six cases that were certainly or probably sarcomatous and seventy-three cases that were certainly or probably carcinomatous. This section may be dismissed shortly for the mean duration of life of the twenty-three fatal sarcomatous cases after the first exposure was seven and a half months and the mean number of exposures was 1.5, while in the fifty-nine fatal carcinomatous cases the corresponding numbers were seven and a quarter months and 1.4 exposures. These differences have no significance. On the other hand there is no case in the sarcoma group parallel to the six cases (four, breast; one, skin of calf; one, tongue) in the carcinoma group that were free from growth and in good health at periods varying from four to over six years after the first exposure to the large quantity of radium and then were lost sight of.

Discussion.—There can be no doubt concerning the potency of a large quantity of radium when used in treatment; the definite and rapid effects manifested by the blood, the dermatitis amounting often to a severe radium burn, the occasional rapid diminution in size of a mass of growth and the

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vomiting that sometimes follows on the exposure are sufficient evidence of the fact. But whether the advantages outweigh the disadvantages is a more difficult question. In my opinion there is little doubt. In spite of the fact that the cases used for experiment were mostly in the latest stages, in spite of the favorable results noted in a few, I cannot but recall the similar experiences when radium therapy was in its infancy and only small quantities of the element were used. The beneficial results noted in the cases under present examination should, I think, be ascribed to radium action as such, apart from the quantity used; the large quantity employed and its nearness to the patient are, in my opinion, accountable for nothing but the grave disadvantages that occurred. Whether use of a large quantity of radium at a greater distance and over longer periods, thus approaching more towards the modern method of prolonged treatment with radium needles and radon seeds, would be efficacious, the present experiments do not indicate. From the financial and technical points of view provision of quantities of radium sufficient to be useful would be formidable. The falling off in intensity of gamma radiation owing to distance and the number of patients to be treated are of an order to increase the difficulties enormously. Were there evidence from the present investigation that the results of such treatment would be outstandingly good, no doubt these difficulties might be overcome; unfortunately, this is not the case.

INTERSTITIAL RADIATION IN METASTATIC CERVICAL NODES OF EPIDERMOID CARCINOMA

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FROM THE SURGICAL SERVICE OF THE MEMORIAL HOSPITAL

IN MAKING a general survey of the treatment of metastatic cervical nodes of epidermoid carcinoma at The Memorial Hospital, we have been impressed by the value of filtered radon implantation in certain of the cases. In view of the possibilities of this form of radium application, a brief discussion of the experiences to date seems to be in order.

A summary of the general plan of cervical-node treatment may indicate more clearly basis of case selection in group at present under discussion.

Since 1916 a conservative surgical plan in the treatment of cervical nodes in cases of intra-oral cancer, a course decidedly at variance with the generally accepted method of routine block dissection, has been followed. The premise that metastasis is by embolism rather than by direct permeation of lymphatics has been accepted. In the adult types of epidermoid carcinoma, at least, involvement of a single node only in the early course of the disease is the rule. With the more embryonal types, this may be followed by other nodes in rapid succession but if so the metastatic deposits tend to be generalized and not necessarily confined to the neck. We believe that up to a certain point at least cervical lymph-nodes perform a conservative function and hence should not be disturbed, if avoidable, particularly in the presence of an active primary growth. For these reasons *routine* dissections, either unilateral or bilateral, have not been resorted to. In the earlier course of the work, a complete unilateral dissection was done in all cases presenting a removable node. These dissections have always been done under local anæsthesia, the technic employed being as radical as possible and at the completion of the operation, and just before closing the wound, radium emanation has been buried at certain of the more dangerous points, particularly where the lymphatic paths were severed.

In the beginning of this work external radiation was very little employed. The unfiltered emanation in glass seeds, or, as they have been commonly called, "bare tubes," represented the only source of effective radiation, and it was coupled with operative surgery. As external radiation became more effective it was employed as a routine procedure in the treatment of all necks in intra-oral carcinoma, as a preliminary step in the treatment program. If no nodes were palpable, the case was kept under routine observation and no other therapeutic measures directed toward the neck. If a metastatic node or nodes, technically removable, were present upon admission or appeared subsequently, a complete dissection was done following the external radiation.

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If the metastatic mass was inoperable external radiation as a palliative measure was continued.

As technical facilities for X-radiation improved, and with added experience in more intensive external radiation dosage, more pronounced effects by way of growth restraint were noted. Certain of the cases showed a much more marked effect than others. Investigation, from a histological standpoint, of the reasons for this peculiar response to radiation in some cases has led to a much clearer understanding of the cellular types of epidermoid carcinoma. Observations on this point by Ewing have led him to apply the term "transitional-cell carcinoma" to a rather large group of the cellular

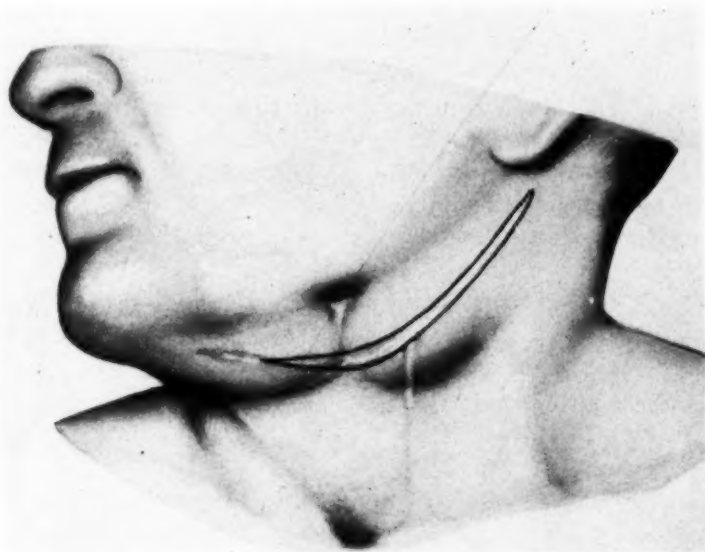


FIG. 1.—Recurrent metastatic neck. Note bulging recurrent mass at angle of mandible with skin fixation anteriorly over lower border of jaw. Heavy line indicates exposure incision by excision of old scar.

epidermoids showing a peculiar response to radiation. To a more limited group, Regaud and Schmencke have applied the term, "lympho-epithelioma."

It is not the purpose of this paper to discuss the histological characteristics of these tumors. The purpose is rather to call attention once more to the fact that recognition of these radiosensitive tumors as definite clinical entities was brought about through first noting their peculiarly favorable response to external radiation. Further clinical study shows that while these undifferentiated growths show a marked local response to radiation they tend to disseminate widely. The local process can be dealt with more certainly by radiation than by operation and, furthermore, the chance of controlling the disease completely by a neck dissection is not great enough to warrant the doing of it. Distant extension, once the cervical nodes are involved, is very apt to occur. Withdrawal of this group, therefore, from the operative class entirely, at once cuts down very considerably the number of neck dissections in our service.

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For several years, radium emanation in the form of a radium emanation pack, which contained from 2,000 to 2,500 millicuries of emanation, in full erythema doses at distances of 6 and 10 centimetres was employed as far as possible. It is only during the past three and one-half years, however, since acquiring the four-gram radium element pack, that we have been able really adequately to carry out this external radium irradiation of the neck. This has added tremendously to the facility and accuracy of the treatment. During the same period there has been marked improvement in the technic of X-radiation. Furthermore, the work of Quimby and Pack has suggested that the combination of X-radiation and radium, externally, was more advan-

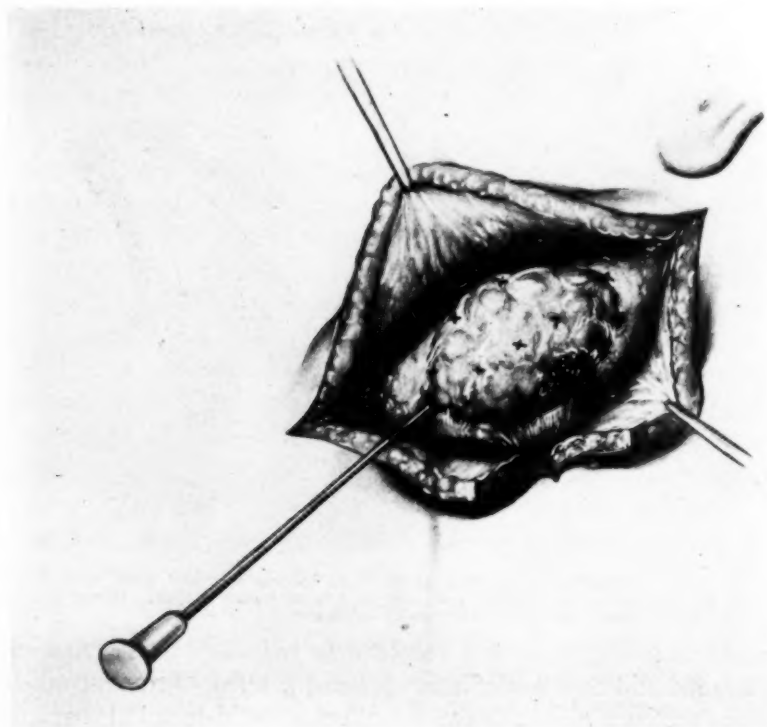


FIG. 2.—Gold tube radon implantation. Note area of necrosis at lower part of metastatic mass.

tageous, quantitatively at least, than the employment of one or the other agent alone. Clinical observations on the combined use of the two agents were responsible for initiating the experimental work of Quimby and Pack and have continued since to substantiate their observations.

At present, therefore, the lymph-node areas of the neck in every case of intra-oral cancer are radiated as promptly as possible after admission to the service. Following this initial irradiation of maximum intensity, unilateral neck dissections under local anaesthesia are done in cases of adult type epidermoid carcinoma presenting clinically involved unilateral nodes with intact capsules and in the presence of a primary growth either controlled already or

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favorable from that standpoint. Bilateral involvement of nodes is considered an indication of inoperability. Perforation of the node capsule is an indication of inoperability. Dissection is not justifiable even in an otherwise operable neck unless the prospect for cure of the primary growth is a reasonable one. It occasionally happens that the patient's general physical condition, for one reason or another, will not permit of a complete unilateral dissection even though all local factors would place the case in that class. As previously stated, we regard the metastatic nodes of transitional-cell carcinomas, in fact all cellular epidermoids, as being more amenable to radiation therapy than to dissection.

The problem next arises as to how best to handle these various cases where dependence must be placed upon radiation in some form. A few of the most radiosensitive epidermoid carcinomas may be cleared up completely by external irradiation providing it is of the maximum intensity that the skin will stand. Assuming a total treatment interval of a month and preferably, perhaps, of a fortnight, not more than $2\frac{1}{2}$ or 3 erythema doses of radiation—whether the most efficient high-voltage X-rays or heavily filtered radium at 6 to 10 centimetres' distance, or both—can be delivered to the lymph-node-bearing areas of the neck. This may take care of the occasional case of particularly radiosensitive character, but beyond this the most that can be hoped for at present is a variable degree of growth restraint.

These gross clinical observations are exactly in accord with the findings of Martin and Quimby in measuring the intensity of radiation in terms of skin erythema doses in a large series of intra-oral carcinomas, taking account of the radiation intensity both at the primary site and in the involved nodes. They have shown that in order to produce complete regression of the adult types of epidermoid carcinoma an intensity of 7 to 10 skin erythema doses is essential throughout the tumor-bearing area and that with the cellular undifferentiated epidermoid carcinomas, the minimum essential intensity varies from 3 to 5 skin erythema doses. Keeping these facts in mind, the problem at once arises as to how best to handle, by way of supplementing the external radiation, the varied group of metastatic nodes classed, for one reason or another, as inoperable. During the years in which unfiltered emanation was used for implantation, attempts were made upon numerous occasions to control otherwise inoperable nodes by direct implantation of bare tubes. In a very few instances the method was successful, but for the most part it failed because of the necrosis which almost invariably followed the use of radiation of this *quality*.

During the latter part of 1924, Failla made possible the collection of emanation in gold capillary tubes employing first a wall thickness of 0.2 millimetre of gold and very shortly changing it to 0.3 millimetre. We have had the advantage of using these filtered radon tubes for interstitial implantation for a full five years. It is this source of radiation which is now used to supplement to the desired intensity the radiation of inoperable metastatic cervical nodes.

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Most of the cases treated have been of palliative character. A certain number, however, as will be noted from the cases assigned to this form of therapy, have, as far as the local process is concerned and viewed from a technical standpoint, been locally operable. This affords some basis at least for comparison, in a general way, with dissection. It is the opinion at present that this combined method of irradiation, with dependence upon filtered radon interstitially for bringing the intensity of radiation up to the desired point, offers a possibility for future improvement in the treatment of the metastatic cervical nodes of epidermoid carcinoma even though external irradiation remains for the most part at a standstill. The trend toward interstitial implantation in metastatic nodes has been gradual. The physical disadvan-

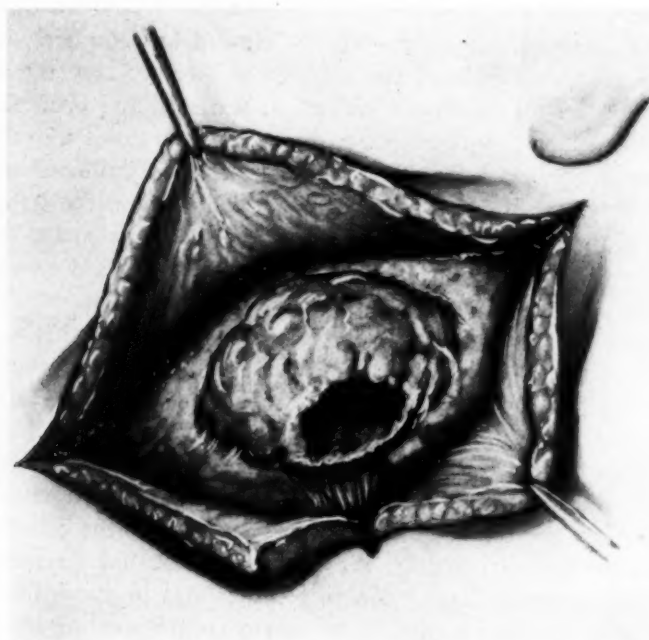


FIG. 3.—Showing necrotic portion of metastatic mass cleaned out preliminary to wound closure.

tages of the old bare tubes have to a large extent been overcome by the present 0.3 millimetre gold filtered radon tubes. Within reasonable limits, an adequate quantity of radiation can be delivered for local control of the growth. The extremely advanced, bulky metastatic nodes are not in a general way suited to treatment by interstitial implantation. As has been shown by Martin and Quimby, a point is reached in the size of the mass under consideration where the relative efficiency of interstitial implantation within the limits of tissue tolerance gives way to external distance irradiation. This is true in the very large, bulky masses of 6 to 10 centimetres or more in diameter, from a physical standpoint alone, and furthermore, there are various additional reasons for refraining from interstitial implantation in these bulky masses,

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particularly the factor of blood supply to the tumor mass and the probability of a wide zone of central necrosis.

The technical procedure of filtered radon implantation is simple. It is done under local anæsthesia and without shock to the patient. While the method aims only at being a form of local treatment, the intensity of the radiation is such that it extends far beyond the limits of any possible local surgical removal. Through local control of a given node, growth is checked and complete or partial bulk regression is brought about. The tumor mass as a source of metastatic emboli is eliminated. Pain incident to the increasing size of an uncontrolled metastatic process is avoided. The broken down, foul, bleeding, fungating tumor masses characteristic of the late stages of uncontrolled metastatic disease in the neck are prevented. In certain of the more favorable cases a reasonable chance for complete control of the growth is offered. If an individual local metastatic process is controlled by this means, and we have proven repeatedly that it can be, then the patient's chance of a permanent result is as good as though that same mass had been removed by a wide margin at least. In making this statement we are not lending support in any sense to the local removal of metastatic nodes or to partial dissections. The fact remains, however, that with the clinical course of the more adult types of epidermoid carcinoma as it is, namely, single node involvement until late in the course of the disease, it is possible that a more limited type of removal is adequate. A review of our neck dissections for metastatic epithelioma of the lip has shown quite conclusively that a submental and submaxillary dissection gives as good results in the entire series of cases as does complete dissection with, of course, much less physical strain on the patient.

Suitable Types of Cases.—The groups of metastatic cervical nodes coming within the range of this combined method of radiation may be enumerated as follows:

1. Adult type of epidermoid carcinomas with perforation of the node capsule and infiltration of surrounding structures.
2. Early involvements of transitional-cell carcinoma.
3. Metastatic nodes, locally operable, but with advanced unfavorable primary growths.
4. Metastatic nodes, locally operable, but in patients of advanced age or in such general physical condition as to render a complete unilateral dissection unduly hazardous.
5. Nodes operable but bilateral.
6. Recurrent nodes.

It will be seen from this that all of those cases falling within our interpretation of cervical-node operability are eliminated. At the other end of the scale, the very advanced cases—either in local bulk of an individual metastatic process or, as more frequently happens, with generalized involvement of nodes—should be eliminated from consideration of treatment by this means. Too much stress cannot be laid on the inadvisability of attempting radical

measures under such circumstances. The moderate degree of growth restraint which might be obtained by external radiation alone will afford to better advantage the small amount of palliative benefit which it is possible to give these unfortunate cases.

Localized masses and, preferably, single nodes, "inoperable" on our basis of appraisal are, of course, most favorable for this form of therapy. The smaller the masses the more favorable they are physically as well as clinically.

Technical Procedure.—In considering the technical procedure, it may be well to repeat that external radiation of maximum intensity, that is, of such intensity as to deliver two or more skin erythema doses within the lymph-node-bearing area, is presupposed in all cases. In some few instances, the metastatic nodes are so located that the trochar radon implantation needles

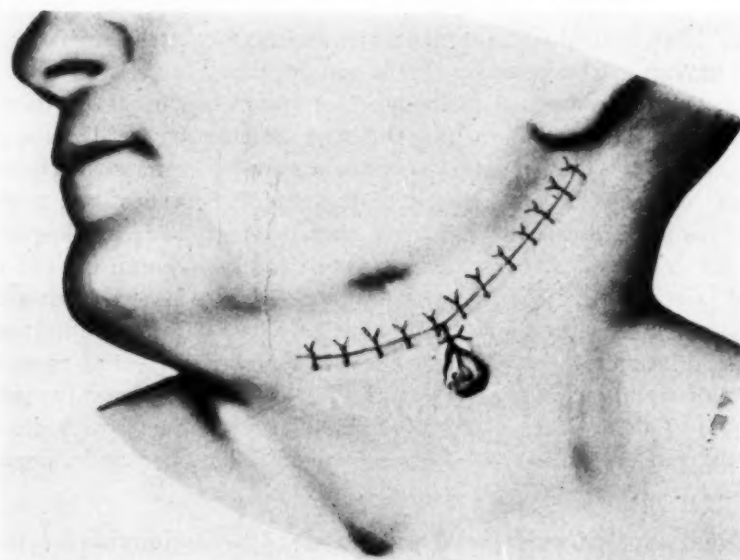


FIG. 4.—Type of immediate closure with drainage below horizontal incision.

may be inserted directly through the skin and into the node. Such insertion is facilitated by simply nicking the skin at one point with a sharp-pointed scalpel and through this the several punctures for gold tube implantation may be made. In general, however, direct exposure of the node under local anaesthesia is decidedly preferable. Practically any metastatic node in the neck can be exposed through an incision a few centimetres in length and extending through the platysma. A very limited amount of dissection after reflecting the platysma is called for—in fact, the least dissection consistent with adequate exposure of the node and immediately adjacent vital structures is preferable. Maintenance of the blood supply to the node and adjacent parts is of very considerable importance when it comes to withstanding the local effects of 6, 8, or 10 skin erythema doses of radiation delivered by this implantation. The exposure not only lends accuracy to the radon implantation but makes possible the avoidance of damage to blood-vessels and nerves lying immedi-

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ately adjacent to the mass or which may be pushed into an abnormal and little-expected position by pressure of the growth.

Direct exposure permits of aspiration of the node for diagnosis after the method advanced by Martin and Ellis. Substantiation of the clinical diagnosis by this means is of very considerable importance in some of the cases and in our experiences has not been dangerous. In a considerable percentage of the cases, the metastatic mass shows some degree of central necrosis and if this, at one point or another, approaches the surface, the subsequent course of the case is benefited materially by draining out this necrotic debris at the time of exposure. The entire area is much less liable to undue inflammatory reaction if this is done.

After the emanation tubes have been implanted, the wound is closed care-

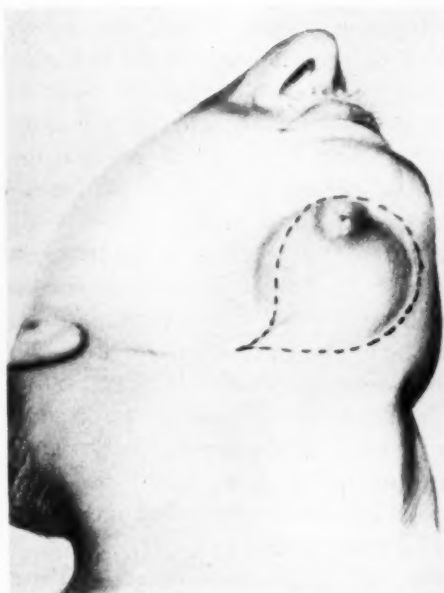


FIG. 5.—Recurrent metastatic node showing skin infiltration, central necrosis, and beginning perforation of skin. Dotted line indicates area of skin to be sacrificed.

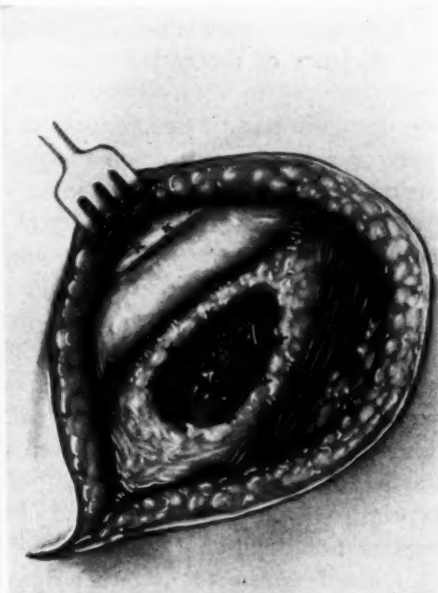


FIG. 6.—Deeper portion of mass infiltrates all adjacent structures and along outer surface of mandible. Areas marked x indicate points of gold tube radon implantation. Central necrotic area has been cleaned out.

fully, particular care being taken in the approximation of the platysma and of the skin. Provision is made for drainage for the first forty-eight hours following operation. No danger is experienced with healing of the wound from the radiation standpoint if the implantation is properly "timed" with respect to the external irradiation. If the external dosage has been delivered within a brief period—a week—then the exposure and implantation may be carried out at once and primary healing obtained before the maximum skin reaction has been reached. While exposure and implantation are not precluded by an intense local reaction, nevertheless, they are inadvisable if they may be avoided. Unless there is some urgent reason for going ahead with it, we favor waiting until the maximum intensity of external radiation has

been passed. Meticulous care should be given the matter of surgical technic at every turn even though the operative procedure is a very small one. If infection is avoided, there will be no trouble, under ordinary conditions, with wound healing. If primary healing is not obtained, the delay in secondary union incident to the intense radiation leaves a very trying wound to deal with for several weeks—a daily reminder of initial carelessness.

In addition to the routine skin preparation, pre-operative painting with 5 per cent. picric acid solution is preferred to iodine. The latter is too irritating on a skin which has been subjected recently to heavy external irradiation. Immediate post-operative dressings of sterile gauze wrung out of alcohol seem to have some advantages over plain sterile gauze and after the stitches have been removed, on the fourth or fifth day, albolene-soaked gauze aids materially in relieving the skin irritation.

One other factor which calls for particular emphasis, in fact, upon which the efficiency of the entire procedure rests, is the intensity of the radiation thus delivered by direct implantation. Reference should again be made to the dosage intensity calculations of Martin and Quimby wherein the adult types of epidermoid carcinoma require a minimum dosage to all parts of the tumor-bearing area of 7 to 10 skin erythema doses, while the more radiosensitive undifferentiated types require at least 3 to 5 skin erythema doses.

This work of intensity measurements was begun as a study in retrospect and later applied to the calculation of doses to be delivered. Our experience has been that unless these factors are adhered to as minimum standards in selecting the total doses for interstitial implantation, the mass in question will not be completely controlled. This method aims at complete local control of growth, even though it be but for palliative purposes. Unless, therefore, full doses by implantation are employed the principle of the method is obviated. Partial control can be obtained by external radiation alone. Unless one expects to obtain complete control of a given metastatic mass, then interstitial implantation of filtered radon should not be resorted to.

Hazards of Implantation Technic.—As with any radiation method, there are certain dangers and hazards attendant upon the interstitial placement of point sources of radon energy of such intensity as those which we ordinarily employ in this procedure—0.3 millimetre gold radon seeds containing 2 millicuries of emanation, or slightly over this amount. We have never experienced the unpleasantness of puncture of large vessels, although it is probable that this would be a very real hazard if blind puncture were done routinely through the skin. Direct exposure of the node avoids this and permits also of placing the emanation tubes a few millimetres at least from the large vessels. With masses infiltrating posteriorly over and about the posterior cervical sensory nerves, care must be taken to keep the emanation tubes several millimetres, if possible, from the nerves in order to avoid a very unpleasant period of pain lasting for several weeks. If this cannot be avoided by this manner of tube placement and the case otherwise warrants it, then section of the posterior sensory roots of the area in question should be done.

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Over-radiation of bone, particularly along the lower border of the mandible, is to be avoided if possible and if this is not possible, one must be prepared to remove a segment of devitalized bone later. This does not always follow directly, but is more apt than not and should be at least counted upon.

Intense radiation by implantation in close proximity to the submaxillary salivary gland is apt to produce a degree of inflammation in the salivary gland which may interfere with its normal drainage and produce, for a transient period, a considerable degree of pain. Since the salivary gland is prone to low-grade infection of mouth origin, this possibility must always be reckoned with and at times drainage provided. Complicating low-grade mixed infection must always be reckoned with in interstitial implantation as in dealing with tumor tissue under other circumstances. Avoidance of it by attention to every detail of careful surgical technic cannot be emphasized too strongly. Once a heavily radiated wound becomes infected and primary healing inter-

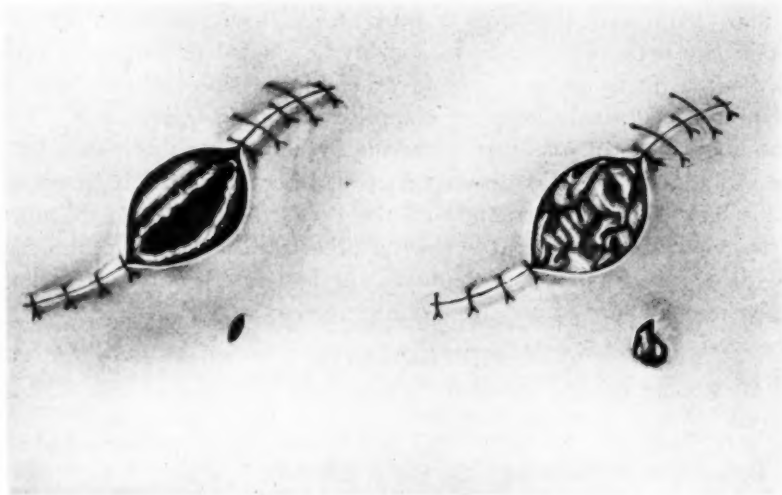


FIG. 7a and b.—Wound only partially closed in order to permit of direct observation, possibly further radon implantation, and removal of sequester. Open wound packed with iodoform gauze and drainage established temporarily below it.

fered with, it is useless to speculate on where the process will end. In the presence of central necrosis of a sizable metastatic node, danger of continued breaking down, out of proportion to that which might otherwise be expected, is a possibility and under such circumstances a reduction in the total implantation dose, at least to the point of minimum safety as indicated by our dosage measurements, is much the safer course. The same is true in principle with fixation and infiltration of skin over the involved node. Unless the questionable area of skin can be sacrificed in making an exposure of the deeper mass, it is doubtful whether such skin will withstand the maximum dosage which we would advocate otherwise.

SUMMARY

Complete control of epidermoid carcinoma, metastatic in the neck, is but rarely effected by external radiation alone. Growth restraint only is the expectancy.

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Interstitial implantation of filtered radon is offered as a means of supplementing external radiation in the control of localized metastatic cervical nodes of epidermoid carcinoma—nodes inoperable for one reason or another, as stated, yet not in all instances technically inoperable. This method, while essentially local in character, permits of adequate quantitative radiation of a metastatic cervical mass unless it be of unusual proportions.

The procedure offers a reasonable chance, we believe, for complete control of growth in a certain number of metastatic nodes outside the group ordinarily adjudged as surgically operable. It offers a maximum degree of palliative control in a large group of the more advanced cases with a minimum of "damage"—either constitutional or to normal tissues immediately adjacent to the tumor-bearing area.

In view of the fact that a localized metastatic mass may be completely controlled by this method of irradiation, operative surgery is relieved of the necessity for attempting extensive operative procedures in cases where the expectancy from such measures is very little indeed. In some, at least, of the metastatic necks which may reasonably be classed as surgically operable, the method has made so far a very favorable impression and may, with added experience, afford a substitute for complete unilateral dissection.

The importance of avoiding deliberate breaking down of tissue by overdosage of radon seeds is stressed particularly because, once it has occurred, especially in the anterior triangle of the neck, the danger of hæmorrhage from the wound, apart from the several other unhappy possibilities, is very considerable. With but few exceptions, the best interests of the patient are served by maintenance of an intact skin covering.

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EFFECT OF IRRADIATION UPON A MALIGNANT THYMIC TUMOR

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ALTHOUGH there is an extensive literature dealing with tumors of the thymus, it is concerned mostly with the pathology and symptoms. Comparatively meagre reports are available of the treatment of choice of such tumors, namely irradiation, and particularly lacking are reports that include autopsy findings in patients that have been treated by irradiation.

The case here presented, believed to be one of thymic carcinoma, was closely followed for two years and two months. An unusually large amount of radiation was employed. Autopsy showed a practically complete disappearance of the tumor from the primary site and from the adjacent regions to which it had extended, evidently a direct result of the heavy irradiation of these areas.

CASE.—S. B. (Hospital No. 39159), a single woman of thirty-nine years, came to the Memorial Hospital January 23, 1928, complaining chiefly of cough and dyspnoea. She stated that she had become ill about one year before. At that time she had suddenly begun to vomit and had noticed a trace of blood in the vomitus. Soon afterward she began to cough, and during the year the cough had become more troublesome and was accompanied by considerable sputum. She had not observed any blood in the sputum. The vomiting had not recurred, but her appetite had become very poor. She had become moderately constipated, but had seen no blood in her stools. She had lost twenty pounds.

For four months she had noticed in her breasts a variable degree of induration, accompanied by the presence of lumps which seemed to disappear from time to time. For six weeks she had had a good deal of difficulty in breathing.

Her family history was negative. Her past history was negative, with the exception of an operation which had been done five years previously for "replacement of a displaced tube," and removal of the appendix. She had had two uterine hæmorrhages, each lasting a week, before this operation.

Upon her admission to the clinic, January 23, 1928, she appeared poorly nourished. The eyes, ears, nose, teeth and oral mucous membranes were negative. In the oropharynx a slight dilatation of veins could be seen.

There was a marked swelling of the superficial veins over the anterior chest wall, extending to the supraclavicular spaces and the neck, and to the upper part of the abdomen. The thyroid gland did not seem enlarged, but the trachea was slightly displaced to the left. The examination of the heart seemed negative. There was a marked increase in the width of the mediastinal dulness anteriorly, and in the degree of dulness. At the base of the right lung anteriorly, a pleural friction rub was heard; while at the base of the left lung the signs seemed to indicate the presence of a small amount of fluid.

In the abdomen, in addition to the engorgement of the veins of the upper half, there was in the right upper quadrant a feeling of fulness and resistance to palpation, suggesting an enlargement of the liver, although the liver's edge could not be felt.

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Pelvic examination was negative.

The blood count gave practically normal findings, as follows: Hæmoglobin 80 per cent., red blood corpuscles 4,480,000; white blood cells 8,800; polymorphonuclear cells 70 per cent.; large lymphocytes 6 per cent.; small lymphocytes 16 per cent.; transitional cells 4 per cent., eosinophile cells 4 per cent.

The röntgenogram of the chest (Fig. 1) showed a large, centrally located mediastinal mass, together with some thickened pleura and fluid at both bases.

A provisional clinical diagnosis was made of either thymoma or mediastinal lymphosarcoma.

Treatment.—The patient's chest was irradiated by means of high-voltage Röntgen-rays, the radium emanation and radium packs as follows:



FIG. 1.—On admission January 23, 1928; showing large mediastinal mass.

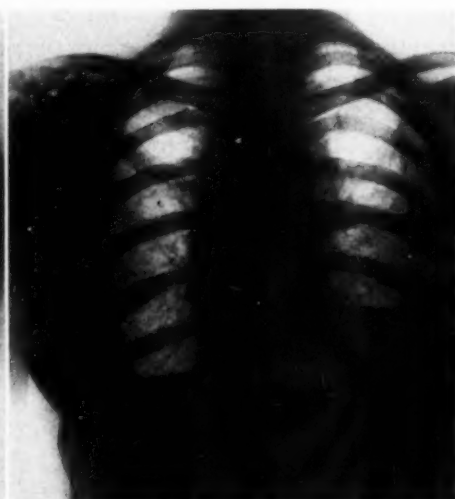


FIG. 2.—A little over four months after admission, showing marked regression of mediastinal mass. There is evidence of thickened pleura and fluid at both bases.

High-Voltage Röntgen Rays

Date	Area	Time (min.)	Kilovolts (peak)	Milli- amperes	Distance (cm.)	Filter
1/26/28	Right chest anteriorly.....	10	185	30	50	0.5 mm. Cu 3 mm. Al
1/28/28	Right chest posteriorly.....	10	185	30	50	0.5 mm. Cu 3 mm. Al
1/31/28	Left chest posteriorly.....	10	185	30	50	0.5 mm. Cu 3 mm. Al
2/ 3/28	Left chest anteriorly.....	10	185	30	50	0.5 mm. Cu 3 mm. Al
2/ 6/28	Right chest laterally.....	10	185	30	50	0.5 mm. Cu 3 mm. Al
2/ 8/28	Left chest laterally.....	10	185	30	50	0.5 mm. Cu 3 mm. Al
6/23/28	Mediastinum anteriorly....	7	185	30	50	0.5 mm. Cu 3 mm. Al
6/28/28	Mediastinum posteriorly....	7	185	30	50	0.5 mm. Cu 3 mm. Al

MALIGNANT THYMIC TUMOR

Date	Area	Time (min.)	Kilovolts (peak)	Milli- amperes	Distance (cm.)	Filter
7/ 2/28	Mediastinum anteriorly	7	185	30	50	0.5 mm. Cu 3 mm. Al
7/ 5/28	Mediastinum posteriorly	7	185	30	50	0.5 mm. Cu 3 mm. Al

Radium Emanation Pack

Date	Area	Millicurie hours	Distance (cm.)	Filter
9/19/28	Mediastinum anteriorly	10,000	10	2 mm. brass
9/20/28	Mediastinum anteriorly	10,000	10	2 mm. brass

High-Voltage Röntgen Rays

Date	Area	Time (min.)	Kilovolts (peak)	Milli- amperes	Distance (cm.)	Filter
12/15/28	Right lower chest anteriorly	4.5	175	30	30	0.5 mm. Cu 3 mm. Al
12/19/28	Right lower chest posteriorly	10	185	30	50	0.5 mm. Cu 3 mm. Al
3/ 9/29	Right lower chest anteriorly, including lower mediasti- num	10	185	30	50	0.5 mm. Cu 3 mm. Al
4/12/29	Right supraclavicular, di- rected toward mediastinum	11	185	30	50	0.5 mm. Cu 3 mm. Al
4/26/29	Left supraclavicular, directed toward mediastinum	11	185	30	50	0.5 mm. Cu 3 mm. Al
5/ 7/29	Mediastinum anteriorly, lower one-half	10	175	30	50	0.5 mm. Cu 3 mm. Al
5/10/29	Right lower chest, antero- laterally	10	175	30	50	0.5 mm. Cu 3 mm. Al
7/29/29	Right chest anteriorly, mid- dle third, obliquely toward mediastinum	10	175	30	50	0.5 mm. Cu 3 mm. Al
8/ 2/29	Right chest posteriorly, mid- dle third, obliquely toward mediastinum	10	175	30	50	0.5 mm. Cu 3 mm. Al
8/ 6/29	Left chest posteriorly, mid- dle third, obliquely toward mediastinum	10	175	30	50	0.5 mm. Cu 3 mm. Al
8/ 9/29	Left chest anteriorly, mid- dle third, obliquely toward mediastinum	10	175	30	50	0.5 mm. Cu 3 mm. Al
10/22/29	Mediastinum anteriorly	10	185	30	50	0.5 mm. Cu 3 mm. Al
10/25/29	Right lower chest anteriorly	10	185	30	50	0.5 mm. Cu 3 mm. Al
10/29/29	Right lower chest posteriorly	10	185	30	50	0.5 mm. Cu 3 mm. Al
11/23/29	Right lower chest laterally . .	10	185	30	50	0.5 mm. Cu 3 mm. Al
11/27/29	Left supraclavicular space . .	10	185	30	50	0.5 mm. Cu 3 mm. Al

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Radium Pack

Date	Area	Milligram hours	Distance (cm.)	Filter
1/31/30	Right chest anteriorly.....	8,000	10	0.35 mm. Pb 1.50 mm. brass
2/ 1/30	Right chest anteriorly.....	4,000	10	0.35 mm. Pb 1.50 mm. brass
2/ 2/30	Right chest laterally.....	7,000	10	0.35 mm. Pb 1.50 mm. brass
2/ 3/30	Right chest posteriorly....	4,000	10	0.35 mm. Pb 1.5 mm. brass
2/ 4/30	Right chest anteriorly.....	7,000	10	0.35 mm. Pb 1.5 mm. brass
2/ 5/30	Right chest anteriorly.....	1,000	10	0.35 mm. Pb 1.5 mm. brass
2/ 5/30	Right chest laterally.....	7,000	10	0.35 mm. Pb 1.5 mm. brass
2/ 7/30	Right chest posteriorly....	8,000	10	0.35 mm. Pb 1.5 mm. brass
2/ 8/30	Right chest laterally.....	1,000	10	0.35 mm. Pb 1.5 mm. brass
2/ 8/30	Right chest anteriorly.....	5,000	10	0.35 mm. Pb 1.5 mm. brass
2/10/30	Right chest laterally.....	8,000	10	0.35 mm. Pb 1.5 mm. brass
2/13/30	Right chest posteriorly....	6,000	10	0.35 mm. Pb 1.5 mm. brass
2/14/30	Right chest laterally.....	2,000	10	0.35 mm. Pb 1.5 mm. brass
2/14/30	Right chest posteriorly....	5,000	10	0.35 mm. Pb 1.5 mm. brass

Course.—Within a month following the first series of röntgen treatments, a marked regression of the mediastinal mass took place, accompanied by a marked decrease of all symptoms and a gain in weight. The dyspnoea disappeared and there was very little cough. The dulness over the mediastinum decreased considerably in extent, but over the lower half of the sternum the percussion note remained definitely flat. The röntgenogram (Fig. 2) still indicated some thickening of the pleura and the presence of fluid at both bases.

Three months later, in June, 1928, the dilatation of the veins over the chest wall and neck had disappeared.

The second series of treatments given during June and July, 1928, was not followed by further improvement. In fact, the cough recurred, and in August, 1928, the film of the chest indicated some extension of the mass into the right lung. At this time the blood count showed moderate anæmia and some leucopenia, possibly the result of the irradiation. Clinically it was soon found that the mediastinal dulness was more marked, and that above the left clavicle there was a definite mass of moderately enlarged, firm, discrete nodes.

Because of these findings, further irradiation was indicated. This time, September 19 and 20, 1928, the radium emanation pack was used because the second cycle of Röntgen-rays had failed to give relief and it was hoped that the tumor would respond better to radium. While some relief did follow the use of the emanation pack over the mediastinum anteriorly it was of short duration. Dyspnoea and cough soon became troublesome again.

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In November, 1928, examination of the chest showed marked decrease of breath sounds over a zone about 10 centimetres in width around the front and side of the right lung at the base, continuous with the area of dullness over the lower half of the sternum. From that time this area of decreased breath sounds persisted practically unchanged. Over this region the percussion note later became dull and this sign also persisted. These findings corresponded with a gradual extension into the right lung as shown by röntgenograms.

During 1929, the patient's condition seemed to change but little. Pain, cough and dyspnoea, while persisting to a moderate degree, did not prevent the patient from continuing to work daily as a stenographer. In April 1929, an enlarged node in the inner part of the right supraclavicular fossa was found. It regressed almost completely following treatment with high-voltage Röntgen-rays. Altogether during 1929 fourteen röntgen treatments were given, mostly about the right lower chest and mediastinum. The patient bore these treatments well. She suffered comparatively little radiation sickness and usually had some symptomatic relief, which was, however, only temporary.

In January, 1930, her symptoms all increased to such a degree that she was compelled to give up work and take to bed. At this time she began to have considerable hæmoptysis. The nodes in the inner part of each supraclavicular space again became enlarged and firm, and for the first time a definitely involved node was found in the right axilla, 1.5 centimetre in diameter. The prognosis seemed hopeless for any further palliation, considering the amount of radiation that had already been used. Moreover the exquisite tenderness of the lowermost ribs in the right side, in the area which had been so heavily irradiated, raised a question of radiation osteitis. However, the severity of her symptoms demanded another attempt at palliation. Accordingly she was admitted to the hospital. This time, January 31 to February 14, 1930, the radium element pack was used over the right chest, over various areas, mostly directed toward the mediastinum. A total of 73,000 milligram hours at 10 centimetres was given. During the course of treatment definite improvement could be seen. The hæmoptysis practically ceased and both pain and dyspnoea lessened considerably. The tenderness of the ribs, however, persisted, but later diminished somewhat following the patient's return to her home.

The enlarged nodes in the supraclavicular spaces and in the right axilla almost disappeared, and some definite clearing of the shadow in the right lung was found on the röntgen film but the dullness and diminished breath sounds previously noted over the lower mediastinum anteriorly and over the right lower chest persisted. In addition a few sonorous râles were heard (March 10, 1930) over the base of the left lung posteriorly.

About March 20, 1930, following the exertion of taking a bath, there was a rather sudden increase of pain and dyspnoea and two days later, March 22, 1930, she died.

Autopsy.—(Done by Dr. F. W. Stewart forty-eight hours after death.) The body, which had been embalmed, was that of a well-developed and well-nourished adult female. There was moderately excessive development of hair in the axillæ and on the upper lip. The pubic hair showed normal distribution. No œdema was seen. No superficial lymph-nodes were palpable. Both breasts were lumpy, and on section showed a diffuse fibrous and cystic mastitis with large cysts, some containing thick fluid. The skin over the right chest wall anteriorly was deeply bronzed.

Thorax.—Both pleuræ were adherent. The tissues in the region of the thymus and the anterior pericardium were thickened and fibrotic, but no gross tumor could be found. The left lung was separated from the chest wall with difficulty. Its pleura was thickened. Its lower lobe appeared to show a partial diffuse consolidation, somewhat obscured by the changes resulting from the embalming. At the base of the left lung toward the periphery was a small semi-necrotic tumor nodule. In the right lung anteriorly was a large empty cavity (Fig. 3) 8 by 6 by 6 centimetres. Its long axis lay longitudinally.

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It extended from near the mediastinum almost to the lateral chest wall. Its walls were hard, fibrous and trabeculated, and contained a very few small nodules, apparently residual tumor tissue. A few trabeculae containing blood-vessels crossed the cavity. The bronchial nodes were large and one contained a semi-necrotic tumor nodule. The bronchi contained faintly yellowish mucus.

The heart was normal. The spleen was slightly enlarged; its markings could not be seen clearly because of the changes caused by embalming. The liver and pancreas seemed normal. The right adrenal contained a small diffuse metastasis to the medulla. The left adrenal was cystic in the centre. The gastro-intestinal tract seemed normal. The lymph-nodes about the celiac axis were enlarged and hard and showed foci of

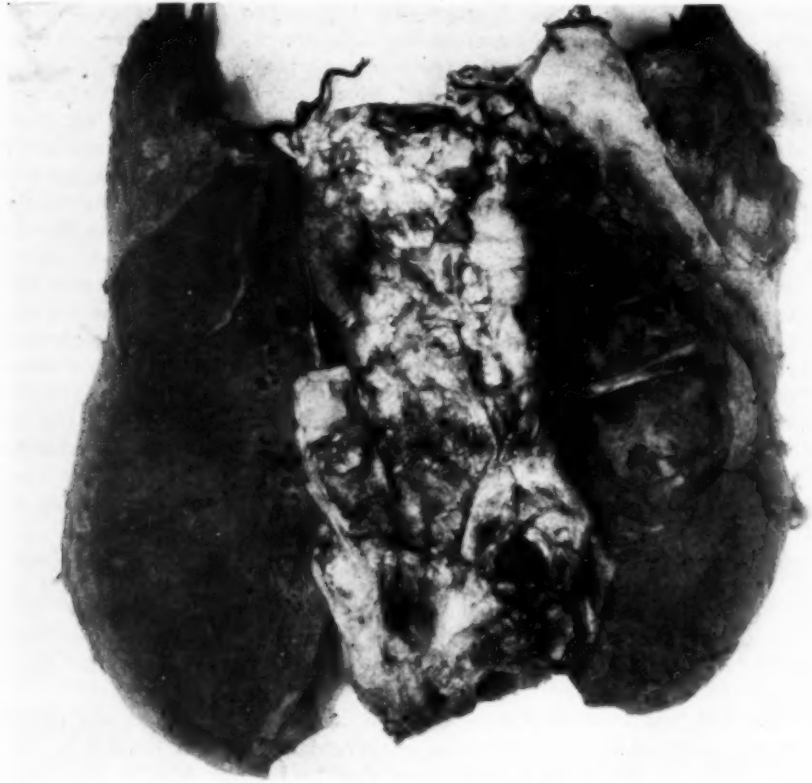


FIG. 3.—Large cavity in right lung.

necrosis. The kidneys were negative. The ovaries were fibrosed and atrophied. The bladder and uterus seemed negative externally and were not sectioned.

Anatomical Diagnosis.—Malignant tumor of undetermined origin; probably thymoma. Metastases to lungs, bronchial and aortic abdominal lymph-nodes and to right adrenal. Pneumonia, fibrous pleuritis, fibrosis of thymic and anterior pericardial regions, atrophy of ovaries, chronic cystic mastitis, enlargement of spleen.

Microscopic Diagnosis.—(Fig. 4.) Doctor James Ewing's report was as follows: "The structure of the tumor is best preserved in the abdominal lymph nodes, where the effects of radiation were less pronounced. Here the sections show a highly malignant tumor process, presenting large round and polyhedral cells, with large hyperchromatic nuclei. There are occasional very large giant cells. Mitotic figures are rather numerous. Many of the areas show many lymphocytes, and here the process suggests a granuloma

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with sarcomatous changes. In most areas the tumor tissue is composed exclusively of large polyhedral or round cells, and here the process resembles carcinoma. The diagnosis seems to be a primary malignant tumor of the thymus arising from the reticulum cells. Since these cells are of epithelial derivation the tumor may be called a thymic carcinoma, but since there are many lymphocytes accompanying the process, it is possible that the disease began as a thymic granuloma, which assumed more malignant properties in its later course."

SUMMARY

A case is presented originally having definite evidence of a large mediastinal mass believed to be a malignant thymic tumor, probably car-

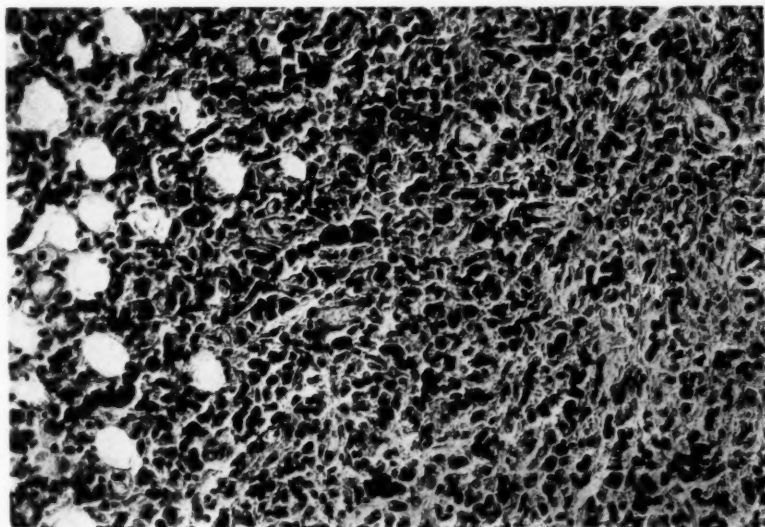


FIG. 4.—Microphotograph of section from an abdominal node.

cinoma, in which treatment resulted in the complete disappearance of all evidence of tumor at the primary site, and in which at autopsy a large cavity with healed walls was found in the right lung anteriorly near the mediastinum. It is believed that this cavity had been the seat of tumor tissue which disappeared as a result of the heavy irradiation with both radium and Röntgen-rays. Various small scattered metastases were found in the bronchial lymph-nodes, the left lung, the right adrenal gland and the aortic abdominal nodes, of which all except the bronchial nodes lay outside of the area that was irradiated.

RESULTS IN THE RÖNTGEN-RAY THERAPY OF GIANT-CELL TUMORS OF BONE

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OF NEW YORK CITY

AT A meeting of the Eastern Section of the American Röntgen-ray Society in January, 1924, the writer read a paper dealing with the effects of Röntgen rays on giant-cell tumors of bone. This article recorded, for the first time, some observations indicating that not only could a majority of them be cured, but in many instances this method was superior to the standard surgical methods of treatment.

It has been suggested that this work be reviewed with the object of comparing the statements made at that time, now more than six years ago, with the information available to date on the present status of those cases.

The majority of the patients studied in presenting that report had been under treatment and observation for three or four years. Several had gone one or two years, and a few about five years, so that a report at this time on the status of those cases, all of which have now gone more than five years since the first treatment, should be of interest in determining the value of X-ray therapy in giant-cell tumors of bone.

The tumors studied which formed the basis for that report were of great variety and location, and although most of them were undoubtedly true benign giant-cell tumors, it may be that in some instances the biopsy findings, along with the clinical history, physical and röntgenographic findings, and course of the disease after treatment, justify a diagnosis of GIANT-CELL SARCOMA, or MALIGNANT GIANT-CELL TUMOR, an expression used lately in some of the reports coming from the Pathological Laboratory of the Memorial Hospital.

The term "giant-cell sarcoma," which was left out of the classification of bone tumors adopted by the Committee of the College of Surgeons for the Registry of Bone Tumors, might have been left in, without seriously impairing the value of this new classification or terminology for bone tumors.

It might be well at this point to state that at times there does appear to be a tumor which possesses some of the röntgenographic and histological features of benign giant-cell tumors, but potentially malignant as shown by subsequent developments.

Stone and Ewing report the occurrence of a giant-cell tumor in the head of a tibia in a male aged nineteen, which, later after curettage, recurrence, and subsequent ineffectual attempts to control the disease, became transformed into a malignant, metastasizing tumor, which caused the death of the patient in spite of an amputation performed before there was any evidence of metastasis to the lungs.

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It is believed that a larger percentage of giant-cell tumors recur after curettage than is commonly supposed. From our experience at the Memorial Hospital it is estimated that about 25 per cent. of all giant-cell tumors recur after curettage. Out of this number a large percentage are giant-cell tumors of the head of the tibia, and in most instances where a malignant transformation developed subsequently, the tumor occurred in the head of a tibia. Just why such an unduly large number of these cases occur in this location has not been explained. It appears, therefore, that the surgical treatment of giant-cell tumors in this location should be altered from the standard procedure of simple curettage and swabbing out of the cavity with carbolic acid or zinc chloride. Adequate pre-operative radiation and the use of a heavy bone transplant might lead to fewer recurrences here and more prompt callus production.

There probably is no other single factor of greater clinical significance in the differential diagnosis of giant-cell tumors than the location. Codman states that one of the requisite factors in diagnosing giant-cell tumors of the long bones is the presence of the tumor in the end of the bone or epiphysis, and not in the diaphysis or shaft. The tumor, he states, must be in, or extend into the epiphysis, or well into the end of the bone. This dictum is not accepted by all observers, and should be qualified when an epiphyseal line is present and the tumor may be in the shaft. An example is demonstrated in Case III.

In those instances where the tumor occurs in an unusual location, regardless of the fact that the history and radiographs are characteristic, it seems wise to exercise considerable care before the tumor is definitely classified as a benign giant-cell tumor.

It seems that mechanical pressure determines to some extent the amount of growth restraint and the degree of malignancy. Tumors that are firmly encapsulated or surrounded by dense, unyielding structures may remain relatively benign from a clinical standpoint for a long time though potentially malignant from a histological viewpoint. In this respect, the location of a giant-cell tumor is an important consideration in the prognosis and treatment.

Case I illustrates some of the above points: This case was so characteristic of a giant-cell tumor from the röntgenographic standpoint that Kolodny cites it as a typical example, but it will be noted that the location is an unusual one for a giant-cell tumor. Two years after this patient's first visit to the Memorial Hospital, and approximately a year after the film was obtained which was shown by Kolodny in his article, another tumor, apparently metastatic from the primary growth in the distal end of the humerus, developed in the ascending ramus of the right inferior maxilla. Although multiple giant-cell tumors do not occur, the appearance of this growth two years after the first tumor appeared in the humerus, makes this conclusion hardly tenable.

Furthermore, the character and location of the subsequent growths strongly indicate that the primary tumor, if a giant-cell tumor, deserves the diagnosis of giant-cell sarcoma.

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CASE I.—Woman, aged sixty-five years, was admitted to the Memorial Hospital in October, 1924. She stated that about six months previously she began having pain in

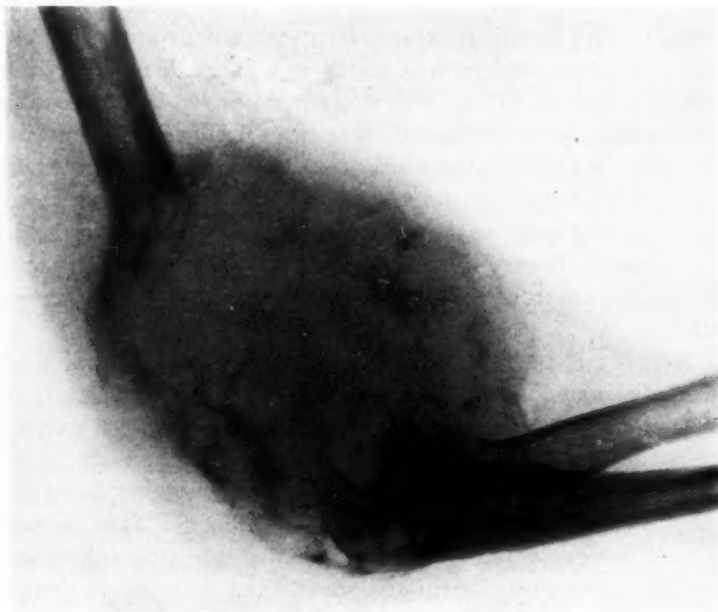


FIG. 1.—Case I. Before röntgen therapy.

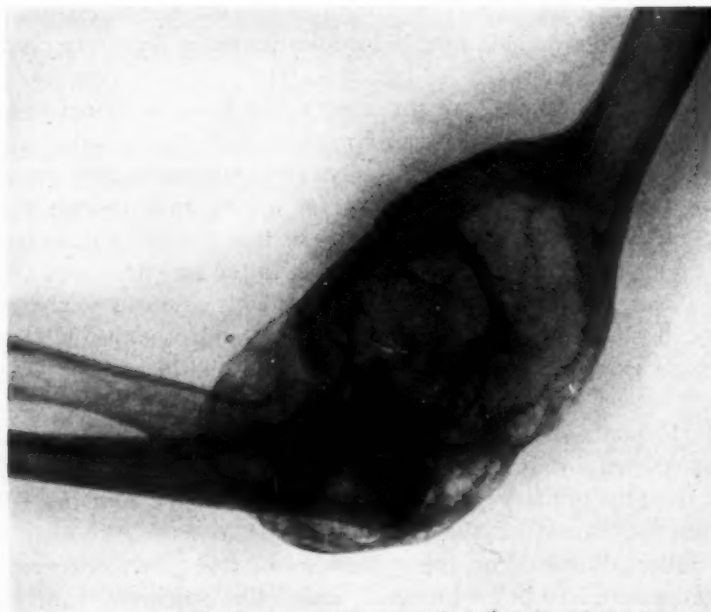


FIG. 2.—Case I. After röntgen therapy.

the right arm and elbow. No history of an injury was elicited. The pain here was followed by swelling which increased rather rapidly. The pain increased in severity and the entire elbow and lower one-half of the humerus, including the forearm and hand.

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finally became markedly swollen and tender. During this period she was treated by her family physician for rheumatism and neuritis. As it became apparent, however, that

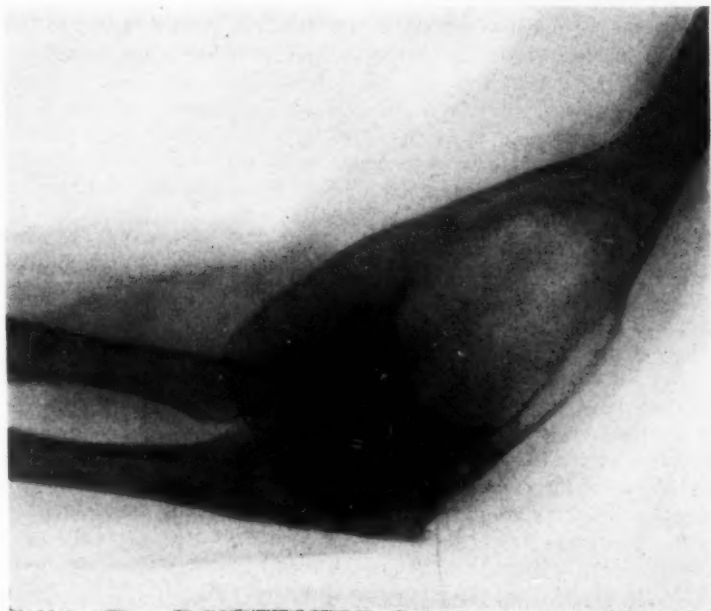


FIG. 3.—Case I. Five year result.

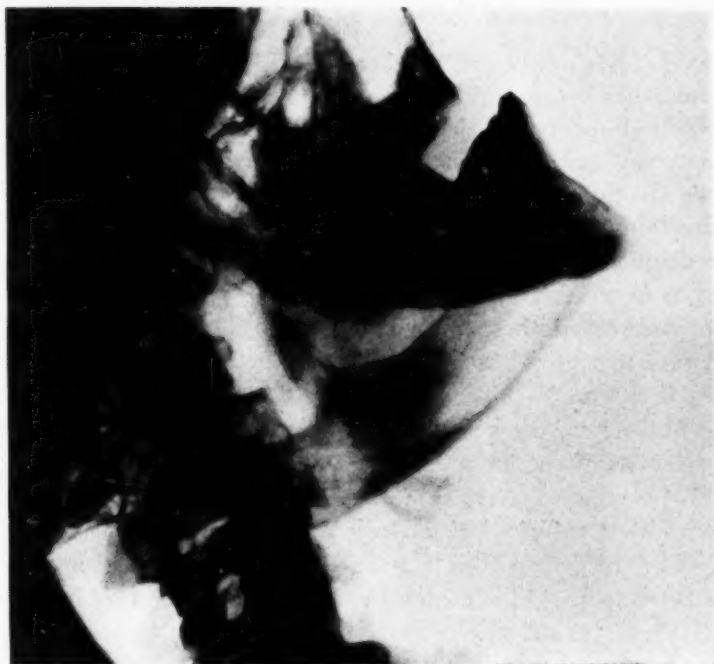


FIG. 4.—Case I. Showing destruction in ascending ramus.

the patient was not improving, she was referred to Doctor Ewing who referred her to the Memorial Hospital.

A film made here on her first visit (Fig. 1) showed a destructive process involving the lower end of the humerus. It appeared to be medullary in origin but of rather rapid growth, dilating the medullary portion of the bone, infiltrating the cortex, and extending out about it into the surrounding soft parts. The tumor responded readily to Röntgen-ray therapy. The pain diminished rapidly, the swelling subsided in the hand, forearm, and arm, then more slowly at the elbow. Films made from time to time reveal (Figs. 2 and 3) definite evidence of bone regeneration. Tenderness and pain finally disappeared and the patient was able to use her hand, wrist, and her elbow to a certain extent. Later on the function at the elbow improved to such an extent that limitation in motion was perhaps only 30 per cent. of normal. This condition continued for about two years when suddenly the patient began experiencing pain in the right side of the face. This was accompanied by tenderness and swelling over the ascending ramus of the right inferior maxilla. A film (Fig. 4) was obtained which showed a large, clean-cut area of bone destruction in the mid-portion of the ascending ramus. A moderately heavy dose of Röntgen-rays was applied here with a very prompt response.

The pain and swelling promptly disappeared and there has been no recurrence here or in the elbow, but subsequent to the appearance of this second tumor, during the past four years, others have appeared approximately from four to eight months apart. One appeared in the right occipital region, another in the sternum, another in the upper end of the left humerus, one in the lower end of the right tibia, and recently, the last to appear, over the sternal end of the right clavicle, and each of these tumors on treatment disappeared promptly and did not recur.

Each of the subsequent tumors developed in a new site. Except for the short periods during the development and treatment of the tumors the patient has been well, up and around, and able to attend to a certain amount of her household duties.

The case is reported (1) because it illustrates an unusual type of giant-cell tumor which we believe should be classified as giant-cell sarcoma or malignant giant-cell tumor, and (2) the palliative value of Röntgen therapy.

That a considerable percentage of error in Röntgen-ray diagnosis of giant-cell tumors occurs is not denied, but routine biopsy to establish the diagnosis, when the clinical history, physical and röntgenographic findings are characteristic, is not only unnecessary, but may lead to infection, dissemination of tumor cells, acceleration of the growth by breaking down the mechanical barrier about it; and furthermore, it not uncommonly happens that when a positive diagnosis is difficult without a section, the report of microscopical findings is as uncertain as the röntgenographic. Also if Röntgen therapy is subsequently employed, the repair process may be hindered and delayed, more deformity may result, and the end-result may not be so satisfactory as if no incision had been made.

The most common sites for benign giant-cell tumors of the bones are found in the ends of the bones, at the knee-joints, and at the distal ends of the radii; but we have seen them in the skull, spine, ribs, pelvis and os calcis, as well as in either end of all of the long bones of the extremities.

The typical röntgenographic features of giant-cell tumors are usually so characteristic as to need little comment. An excellent example is to be found in Case II (Figs. 5, 6 and 7).

CASE II.—Man, aged twenty-eight years, first began to experience pain in the left knee, especially after walking. This persisted and gradually became worse so that the patient was unable to walk without a limp. About July, 1922, he was given ultraviolet

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Fig. 5.—Case II. Before Röntgen therapy.



Fig. 6.—Case II. During Röntgen therapy.

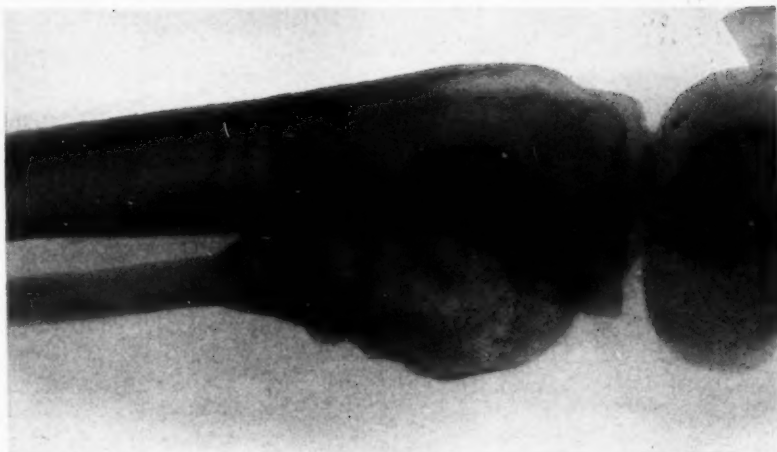
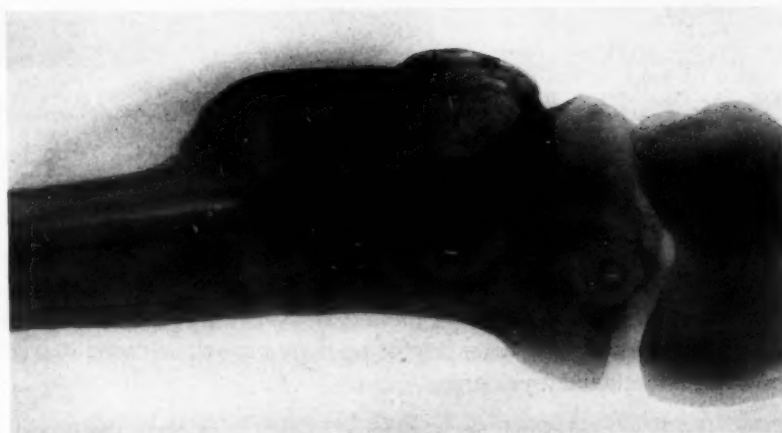


Fig. 7.—Case II. Seven years after treatment.



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ray treatment by his physician who thought the condition was rheumatic. Later the patient noticed a swelling at the site of the pain. This increased in size, and the pain persisted. The patient was finally referred to the Memorial Hospital where he reported in March, 1923. The films reveal classical features of a giant-cell tumor. The first Röntgen-ray treatments were followed by some reaction as the dose was fairly heavy. The pain and aching diminished and the tumor became firm on palpation. Films made later on reveal evidence of beginning ossification.

At the present time the tumor is entirely healed, bony hard. The patient has no symptoms, walks without a limp, and there is no impairment in function of the knee. This is a seven-year cure.



FIG. 8.—Case III. Before Röntgen-ray treatment. (Anterior view.)



FIG. 9.—Case III. Before Röntgen-ray treatment. (Lateral view.)



FIG. 10.—Case III. Three months after last X-ray treatment. (Lateral view.)

The tumor occurs in an end of a long bone. It is medullary in origin and symmetrical in growth, dilating equally in all directions the medullary portion of the bone, and thinning out the cortex. A characteristic trabeculated appearance is present. The tumor does not extend for any distance through the medullary cavity, and does not extend along the cortex destroying it, and does not infiltrate the soft parts, producing bony growth as noted in osteogenic sarcomas or endothelial myelomas.

CASE III.—Boy, aged eleven years, referred in July, 1925, from the Brooklyn Hospital, with the history that in November, 1923, he sprained the left wrist. Two months later he again injured the left forearm. Two months later the wrist began to pain and

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a swelling was noted over the lower end of the radius. A physician was consulted who treated it with massage and put the forearm in a splint for three weeks. In April, 1924, a biopsy was done and soon afterward an operation was performed which consisted of curettage, cauterization and insertion of a substantial bone transplant. Three months later the wrist began to pain and later an enlargement was noted. This persisted off and on for several months, then began to increase. The patient consulted a physician at the Brooklyn Hospital and from there he was referred to the Memorial Hospital for Röntgen-ray treatment.

The examination here disclosed a tumor mass in the lower third of the left forearm



FIG. 11.—Case IV. Before Röntgen therapy.

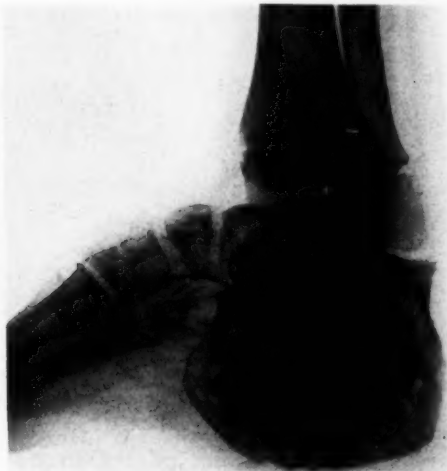


FIG. 12.—Case IV. Five years after Röntgen therapy.

about three times the size of the opposite or normal wrist. The Röntgen-ray films obtained reveal the location, size, and extent of the recurrence. They also show that the bone graft has been completely destroyed. Röntgen-ray therapy was started and only four treatments were given—two in October and two in December. Each exposure was a suberythema dose. No reaction was obtained and instead there was a continual decrease in the size of the tumor which, by the first of January, 1925, or three months after the patient's first visit here, was so marked that it was decided to discontinue treatments, keep the patient under observation, and obtain films from time to time. These demonstrate the effect of radiation and the effort at bone regeneration.

This case demonstrates several of the statements made above: First, that giant-cell tumors occur in the shaft when an epiphyseal line is present, and not in the epiphysis as stated by Codman, but perhaps of greater importance is the demonstration of superiority of radiation over surgery in the treatment of giant-cell tumors located here. Those who have seen the surgical results of treatment of giant-cell tumors here in the lower end of the radius are impressed first by the large number of recurrent tumors after curettage, and secondly, by the marked deformity resulting from subsequent curettements and by the large number of cases which finally require resection and bone transplant. In many instances, although the patient is cured of the tumor, a marked deformity of the wrist-joint results and the function of the

wrist and hand markedly impaired. It is felt that although failures in the Röntgen therapy of the giant-cell tumors in this location have been reported, these cases should all be treated by Röntgen-ray therapy first before an operation is resorted to. The only recurrence of a giant-cell tumor after radiation in our series of cases was a tumor which occurred in the lower end of the radius. The recurrence, however, was treated successfully, and the patient has now gone five years since the recurrence was treated, with no evidence of the disease at the present time, and a good functional result at the wrist (Figs. 7, 8 and 9).

CASE IV.—Boy, aged five years, admitted to the Memorial Hospital from the New York Orthopedic Dispensary and Hospital in November, 1924 with the history that about two and one-half years previously he was seized with pain in the left heel. Some swelling was noted and the foot and ankle were put in a plaster case for three months. The condition continued to get worse, and the leg was then put into a brace. This, however, did not improve conditions and the patient was referred here where X-ray films were made. These revealed extensive destruction of the os calcis. The heel had so enlarged that it was approximately the size of a large orange, extremely tender, the skin tight and reddened. The patient could not walk. The destruction was so extensive that it was difficult to feel sure as to the nature of the process. It was believed that even though the tumor were of a benign nature, or a giant-cell tumor, if Röntgen therapy succeeded in controlling the growth the deformity of the foot would be so great that it would probably be useless as a weight-bearing structure.

The patient's mother was advised to submit the child to an amputation. This she refused to do and insisted that Röntgen therapy be tried. The response to the first two treatments was prompt and satisfactory. There was first relief from pain; next, a progressive but slow diminution in size of the tumor was noted; it became firm to touch and the tenderness disappeared. (Figs. 11 and 12.) At the present time the patient walks without any difficulty. He is able to stamp his foot down on the pavement without pain and it is believed that by the time he reaches manhood, through the normal growth of the foot, the comparative deformity will be very little. This is a six-year cure.

CASE V.—Man, aged twenty-two years, came to the Memorial Hospital in May, 1920. In July, 1918 he fell and twisted his leg which caused a great deal of pain in the left hip. He was not able to be up and about for a week. Since that time he has had several similar injuries, all of which, although some of them have been slight, caused a great deal of pain and some disability. The aching finally became fairly constant, and was especially severe after hard work, heavy exercise, and walking. It was impossible for him to sit long with comfort, and he was unable to sleep on his left side. Finally he noticed definite enlargement of the left hip.

Examination revealed a rather smooth, regular enlargement of the ramus of the left ischium, and on rectal palpation a definite bulging through into the pelvis was palpated. The films of the pelvis made on his first visit reveal evidence of a diffuse destructive process, apparently medullary in origin, involving the ischium and extending up into the ilium back of the acetabulum, where it bulged through into the pelvis. A faint line is noted here, indicating its extent in this direction.

Although this tumor was classified as a giant-cell tumor, the film shows a destructive ability not ordinarily possessed by the benign giant-cell tumors. If this tumor were located in the shaft of a long bone it would probably be classified as an endothelial myeloma or a Ewing's tumor.

The first two Röntgen-ray treatments were followed by a gradual relief from pain. The swelling slowly subsided, and the subsequent films showed a beginning and a progressive effort at bone regeneration. The patient was able to return to his occupation

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FIG. 13.—Case V. Before Röntgen therapy.



FIG. 14.—Case V. Ten years after Röntgen therapy.



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within six months, and has continued at work since that time. He has no limp and no limitation in motion at the hip-joint. The films show that the tumor has become densely ossified. This is a ten-year cure and demonstrates the usefulness of Röntgen therapy in inoperable bone tumors, inoperable from the standpoint of location and extent (Figs. 13 and 14).

CASE VI.—Man, aged thirty-seven years, was referred to the Memorial Hospital March 27, 1924, from the Mary Immaculate Hospital in Jamaica, New York, with the history that in July, 1920, he fell and struck the right knee. He was off duty for three weeks. Two to three years later he again injured the knee and was off two weeks. In



FIG. 15.—Case VI. Before Röntgen therapy. (Anterior view.) FIG. 16.—Case VI. After Röntgen therapy. (Anterior view.)

February, 1924, he wrenched the knee while working and since that time has been unable to return to duty. At the Memorial Hospital films which were made revealed a destructive process in the lower end of the femur (Fig. 15). It extends down to the joint surface of the condyles, is approximately the size of an orange, and only a small portion of normal bone remains in the distal end of the femur along the inner side of the cortex above the inner condyle.

Röntgen-ray therapy was followed by relief from pain; the soft-parts swelling slowly subsided; the tumor became firm on palpation and the X-ray films made later (Fig. 16) from time to time demonstrate a continuous effort at bone regeneration.

This case illustrates the results obtainable in the treatment of giant-cell tumors of the lower end of the femur. It is a six-year cure. Attention should be directed especially to the function of the knee-joint. It will be seen that the joint space is normal in width

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and contour and that no deformity here or in the distal end of the femur has occurred. There is no limitation in motion and the man is working at the present time—occupation, boilermaker.

CASE VII.—Man, aged twenty-four years. No trauma in history. The trouble began with pain and aching at the knee, which became quite severe, especially at night, when he had been on his feet a great deal during the day.

Films revealed a large area of destruction in the anterior part of the lower end of the left femur (Fig. 17). Although the process lacks the clean-cut, trabeculated appearance of a benign giant-cell tumor, it was felt that these features were absent owing to



FIG. 17.—Case VII. Before Röntgen therapy. (Lateral view.)



FIG. 18.—Case VII. After Röntgen therapy. (Lateral view.)

the rapid growth of the tumor. There was some disagreement as to the diagnosis. The response to Röntgen-ray therapy was prompt. The pain was relieved and the swelling diminished. The tumor became firm to touch and the radiographs (Fig. 18) made later showed an effort at bone regeneration.

These cases of patients with giant-cell tumor in the lower end of the femur are the most important and most satisfactory group. Very frequently the surgical results here are in comparison quite unsatisfactory. Deformity of the joint surface and limitation in motion is common following curettage, and if recurrence takes place or infection develops, these commonly lead to amputation. In all of the cases of giant-cell tumor in the distal end of the femur which we have treated, the tumors were so large that had a curettage

been performed only a shell of the bone would have remained, insufficient for weight-bearing purposes. It has been stated that although the Röntgen-ray may cure giant-cell tumors the period of disability necessary for bringing about firm callus production is so great that surgical treatment is preferable. In the beginning of this work in 1920 that statement seemed to be true, but since 1925, with improvement in technic and the administration of light doses, this statement no longer holds. With the exception of one case, our last five cases of giant-cell tumors of the distal end of the knee have been allowed to be up and around some with the use of a walking Thomas splint, and following their usual occupation, and there has been no real period of disability from the time that treatments were started. It is believed that this is partly responsible for the rapidity of bone regeneration. The patient who is kept flat on his back in bed with the knee immobilized in plaster splints is certainly not going to show so prompt callus production.

Treatment.—The question is frequently asked, "What is the dose you employ in the treatment of giant-cell tumors?" The answer is rather unsatisfactory, for there is no standardized method of irradiating these tumors. There is no Röntgen-ray dose. The amount of radiation given to the tumor and the methods of delivering it vary with the case, so that the answer to this question usually is, "It varies with the case."

Few of these tumors respond alike to the same dose of Röntgen-rays. Radiosensitivity varies, as does that of other tumors, with the presence or absence of many factors, which include age of the patient, location of the tumor, rate of growth, and the local effort at growth restraint.

As in other instances, the more cellular, rapidly growing, or malignant a tumor may be, the more prompt is its response to radiation; and frequently the safest plan to follow in Röntgen-ray therapy is first to apply a test dose. In the majority of instances these tumors are comparatively radiosensitive, and seldom is it necessary to employ massive, high-voltage doses. Heavy doses are frequently followed by a severe reaction characterized by redness, swelling, tenderness, pain with an actual expansion of the tumor itself, as shown in the radiographs. In the beginning of this work we believed that this was essential in obtaining a favorable result. We have since found that owing to the susceptibility of these tumors, they can be destroyed through the application of lighter doses which are not followed by this extreme degree of reaction. Bone regeneration seems to follow more promptly when lighter doses are employed. Furthermore, during the severe stage of reaction fracture may occur, and the accompanying pain produces contraction of the muscles, and the tumor may be telescoped over the end of the shaft of the bone in which it occurs.

Special care should be taken during the early stage of the treatment of these tumors to protect the part from injury, and especially to protect the tumor from pressure in a weight-bearing limb, but it is seldom necessary to apply plaster splints, or to hospitalize the patient. Patients have been allowed to be up and around with the use of a walking Thomas splint or

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crutches. Later these have been withdrawn and the patient allowed to be about with a cane, and several have gone on earning a living during the period of active treatment.

In the knee-joint cases, and this is the most important group from the practical standpoint, we have given on the average eight or ten treatments, a series consisting of three exposures, the exposures from three or four days to a week apart, the portals consisting in the external, anterior and internal surfaces, using the so-called low voltage technic, 140 kilovolts, 4 milliamperes of current, 4 millimetres of aluminum filters, 12-inch target skin distance, and from 12 to 15 minutes' exposure. An interval of approximately six weeks to two months is allowed to elapse before these treatments are repeated; but a great deal of variation occurs in the dosage and methods of delivering it. The röntgenologist must himself determine the amount to be given in each case at each treatment, and the decision as to how much to give and when to give it can be arrived at only through careful questioning of the patient, examining the part under treatment, and inspection and comparison of the radiographs obtained from time to time.

Patience is essential. A good case for Röntgen therapy with conditions present insuring a good result may be badly damaged through haste and the application of too many heavy doses given too closely together, and our failures to obtain prompt and satisfactory results have often been for this reason. In other instances where Röntgen-ray therapy failed to control the growth and bring about satisfactory ossification we later learned that the original diagnosis of giant-cell tumor was wrong, and that we were really dealing with a malignant atypical bone sarcoma, or a metastatic process. However, it appears that sufficient time has elapsed and the number and variety of cases are large enough to warrant the conclusion that the optimistic statements made in the article referred to above, published in 1924, were fully justified as shown by the course of the above cases since that time.

The writer desires to express his gratitude for the support, encouragement, and advice given by Dr. James Ewing in the earlier stages of this work, without which it probably would not have been undertaken. And no doubt many of those cases under X-ray treatment during that period would have subsequently been operated on, some for amputation, before the final Röntgen-ray results were demonstrable, had it not been for his repeated insistence that sufficient time must be allowed to elapse in each case before the ultimate effects of Röntgen-ray therapy could be determined. Often during the stage of reaction to Röntgen therapy, the appearance of the tumors suggested increased activity of the growths. At other times for over a period of weeks there would be no demonstrable evidence of the beneficial effects of radiation, and no evidence of ossification apparent. It is during such periods that patience is essential. Resorting to surgery or to further radiation, as stated before, may prevent results which might otherwise be very satisfactory.

RÖNTGEN THERAPY IN CARCINOMA OF THE BREAST

A STATISTICAL STUDY OF 977 PRIVATE CASES

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WE HAVE confined our studies to private cases, because until recently it has been impractical to follow the dispensary cases in the hospitals. We have found private cases very much more coöperative. The 977 cases forming the basis of this study include those patients who were treated between June, 1902, and June, 1927, or a total period of twenty-five years. The last cases in this series have been treated more than three years ago.

Thirty years ago, an individual case of cancer which was cured by X-rays excited much interest. Since then, almost every practitioner has seen the disappearance of cancer in some part of the body, so that now we have become more interested in the general or relative value of the X-rays in various types or locations of cancer. This has led to the preparation of statistics. Most observers dealing with cancer also have seen primary, recurrent, and metastatic carcinoma of the breast disappear as a result of radiation treatment, and enough cases have now accumulated to be of some value as statistics. Unfortunately, any statistical study of radiation in carcinoma of the breast today must include the results of a developing and variable technic. It must always be remembered that technic and clinical judgment count for as much in radiology as in surgery. Better results are being produced today than were produced even ten or five years ago.

A statistical study of the therapeutic results in carcinoma is always difficult because of the variable factors involved and the great difficulty of classification. Unfortunately, the great majority of patients with carcinoma of the breast who are referred to the radiologist are in the inoperable and very advanced stages. Dr. W. J. Mayo says: "In this type of case, radiotherapy is at its best a triumph and a despair. It often does so much good that the patient and the family begin to look for a cure, but failure is the result, and radiotherapy is unjustly brought into disrepute for a meritorious performance."

A direct comparison with surgical statistics is difficult because very few primary cases have been referred for radiation treatment. In the great majority of instances, as the subsequent statistics will show, only the inoperable cases have been referred for primary treatment, and only the more advanced cases for post-operative treatment. Recurrent carcinoma, which

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makes up a great part of our cases, is not even included in the usual surgical statistics.

The great variation in the extent of the disease, either primary or recurrent, together with the variability in the degree of malignancy, and the sensitivity to radiation, makes classification extremely difficult. We have, therefore, made use of numerous tables to determine the value under variable circumstances. It is well known that in all surgical clinics many patients are not treated at all because they are beyond any surgical relief, and therefore are not included in surgical statistics, while practically all cases are treated by radiation and we have, therefore, included all.

In most surgical statistics, the cases are classified on the basis of operability. Practically all surgeons, today, consider tumor tissue which is movable and confined to the breast as operable. Most surgeons still consider carcinoma which has invaded only the axilla as operable, but practically none consider a case with supraclavicular involvement as operable.

The end-results are affected not only by the extent of the disease, but by the type of cancer, the rapidity of growth, the age of the patient, the extent of metastasis, the regions invaded, the physical condition of the patient, the duration of the symptoms before operation, or the duration of the recurrence before radiation is begun and the time interval between operation and post-operative treatment. We have, therefore, taken these factors into consideration so far as is practical in making up these statistics. We have previously made statistical reviews of our breast cases in 1925, 1928, and 1929. We are now bringing this review up to June, 1930. In our previous reviews as well as in this review, we counted as dead all patients that could not be traced. Since the 1925 report and in each subsequent report, we have been able to trace some of the missing cases. This has made an improvement in our percentage values. When patients could not be traced we have counted them as living only to the date of our last record.

As shown in the 1929 study we have not found the grading of tumor tissue as to the degree of malignancy as shown by the routine microscopical sections to be of value in making a prognosis (Table I).

TABLE I
Sex, Social Status, and Location

	Number	Per cent.		Number	Per cent.
Males.....	12	1.2	Married.....	742	76
Females.....	965	98.8	Single.....	235	24
Total.....	977	100.		977	100
	Right breast involved in 455 cases or 46 per cent.				
	Left breast involved in 469 cases or 48 per cent.				
	Both breasts involved in 53 cases or 6 per cent.				
	Total	977		100 per cent.	

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This table shows that while carcinoma of the breast in males is rare, it still makes up over 1 per cent., and, since 6 per cent. of the cases show involvement of both breasts, the presence of a tumor in each breast does not rule out carcinoma.

TABLE II
Conditions Which First Attracted Attention to the Tumor

Lump	55 per cent. of cases	} 91 per cent.
Pain	21 per cent. of cases	
Injury	15 per cent. of cases	

The remaining 9 per cent. gave as the first complaint the following symptoms:

Stinging sensations.	Tender axilla—neck.
Eczema of nipple.	Dimpled skin.
Bleeding nipple.	Sinus in breast.
Discharge from nipple.	Pigmented mole.
Ulceration of nipple.	Pain right under abdomen.
Soreness in nipple.	Rheumatism in back, <i>etc.</i>
Retraction of nipple.	Swollen arm.
Increase in size of breast.	Cough.
Lump in axilla.	Dyspnoea.
Lump in neck.	Cachexia.
Abscessed breast.	Anæmia.

This table shows, of special importance, that a lump or pain is the first symptom in 76 per cent. of the cases, and that traumatism should lead to a careful examination and follow-up if negative. It also shows that any of the twenty-five symptoms mentioned should lead the physician to make a careful examination of the breasts.

TABLE III
Time Intervening Between the First Symptom and Active Treatment by Either Operation or Radiation
(Average 16.2 months)

Time	Cases	Time	Cases
1 month	103	2 years.....	110
2 months.....	95	3 years.....	107
3 months.....	41	4 years.....	22
4 months.....	60	5 years.....	20
5 months.....	67	6 years.....	12
6 months.....	68	7 years.....	7
7 months.....	39	8 years.....	8
8 months.....	22	9 years.....	4
9 months.....	11	10 years and over.....	3
10 months.....	22		
11 months.....	23	Total.....	960
12 months.....	116		

No record in seventeen of the cases.

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The average duration of symptoms during 16.2 months before operation or radiation in the 960 cases in which this fact is recorded shows, in general, the advanced type with which we have dealt. It should also stimulate us all to make more of an effort to educate the public and the profession as to the early symptoms of cancer of the breast, and the importance of skillful and active treatment at once. It is rather discouraging to note that only approximately 69 per cent. received active treatment within twelve months, and 10 per cent. within one month. It must also be noted that all of these cases were treated more than three years ago. We note more alertness now.

TABLE IV
Age Incidence

Years	No. of cases	Years	No. of cases
16.....	1	55 to 60.....	96
18.....	1	60 to 65.....	104
20 to 30.....	24	65 to 70.....	50
30 to 40.....	125	70 to 75.....	38
40 to 45.....	161	75 to 80.....	18
45 to 50.....	192	80 to 85.....	8
50 to 55.....	159		

65.2 per cent. of all cases between ages of thirty and fifty-five. Only 2 $\frac{3}{8}$ per cent. were under thirty years of age. Total 977 cases.

TABLE V
Average Time Duration from Operation to Recurrence
(One Year and 7 Months)

Recurrence within	Cases	Recurrence within	Cases
1 week.....	4	12 months.....	40
2 weeks.....	10	1 $\frac{1}{2}$ years.....	33
3 weeks.....	8	2 years.....	39
4 weeks.....	34	3 years.....	21
5 weeks.....	3	4 years.....	20
6 weeks.....	5	5 years.....	9
7 weeks.....	1	6 years.....	7
8 weeks.....	21	7 years.....	6
3 months.....	21	8 years.....	6
4 months.....	29	9 years.....	2
5 months.....	16	10 years.....	3
6 months.....	27	11 years.....	1
7 months.....	14	12 years.....	1
8 months.....	11	13 years.....	1
9 months.....	11	15 years.....	2
10 months.....	10	18 years.....	1
11 months.....	2		
		Total.....	419

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Recently, a woman discovered a tumor in her breast at 8 A.M.; and at 10 A.M. she was in the surgeon's office and at 11 A.M. she was in our office for radiation treatment because the diagnosis was mastitis, and now she is well.

It is to be noted that approximately 64 per cent. of the 419 cases had their recurrences within a year, while the latest recurrence occurred after eighteen years. This patient was operated upon eighteen years previously by Dr. W. W. Keen and was referred for treatment of the recurrence by Doctor Keen and Dr. John B. Deaver. At the time of the recurrence in the right breast, a tumor had also developed in the left breast, which was amputated by Doctor Deaver five weeks before coming to us. There was a recurrence in the operative scar on the left also, showing that the resistance to cancer was at a low ebb. The recurrences showed marked reduction after radiation but the patient was seventy-seven years of age and died of cardiac disease four months after beginning treatment. This table also shows that there was a total of thirty cases out of four hundred and nineteen, or approximately 7 per cent., in which the recurrence occurred more than five years after operation.

TABLE VI
*Time Interval Between the First Sign of Recurrence and the Beginning of
Radiation Treatment*
(Average 6.6 months)

Time	Cases	Time	Cases
2 weeks.....	10	8 months.....	9
3 weeks.....	12	9 months.....	9
4 weeks.....	58	10 months.....	3
5 weeks.....	4	11 months.....	2
6 weeks.....	11	12 months.....	64
7 weeks.....	3	1½ years.....	11
8 weeks.....	63	2 years.....	10
3 months.....	50	3 years.....	3
4 months.....	19	4 years.....	3
5 months.....	25	5 years.....	4
6 months.....	35		
7 months.....	11	Total.....	419

This average delay of 6.6 months in obtaining radiation treatment seems unwise and unnecessary. It would seem that the delay is either due to a lack of follow-up inspection, or too great assurance given to the patient that there will be no recurrence, or that the surgeon is unwilling to recognize the recurrence.

Based upon our observations it would seem that if these patients had all received routine, thorough and skillful post-operative irradiation, beginning within two or three weeks after operation, nearly all could have avoided at least a local recurrence. One cannot always avoid metastasis, because distant metastasis may have taken place long before the operation.

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TABLE VII

Average Time Intervening Between Operation and Röntgen Treatment in Recurrent Group
(Average 22 months)

Treatment started	No. of cases	Treatment started	No. of cases
3 weeks.....	4	1½ years.....	49
4 weeks.....	7	2 years.....	41
5 weeks.....	1	3 years.....	30
6 weeks.....	6	4 years.....	20
7 weeks.....	5	5 years.....	17
8 weeks.....	25	6 years.....	6
3 months.....	24	7 years.....	6
4 months.....	21	8 years.....	6
5 months.....	23	9 years.....	2
6 months.....	21	10 years.....	3
7 months.....	11	11 years.....	1
8 months.....	18	12 years.....	1
9 months.....	8	13 years.....	1
10 months.....	12	15 years.....	2
11 months.....	7	18 years.....	1
12 months.....	40		
		Total.....	419

Table VIII shows seventy-nine cases in which there were one or more operations for recurrence before being referred for irradiation of the new recurrence. Of this group, twenty-seven, or 34 per cent., of the cases remained well three years, and fifteen, or 19 per cent., of the cases remained well five years and over. This would seem to indicate the advisability of thorough irradiation locally and in the adjacent tissues where metastases are

TABLE VIII

Showing Operations for Recurrences Before Being Treated by Irradiation

39 cases, 1 operation before second recurrence
23 cases, 2 operations before third recurrence
8 cases, 3 operations before fourth recurrence
5 cases, 4 operations before fifth recurrence
4 cases, 5 operations before sixth recurrence
Total 79 cases

likely to be found as a routine post-operative procedure, but especially at the earliest sign of recurrence. A 39 per cent., three-year, and a 20 per cent., five-year salvage after one or more operations for recurrence is pretty high.

The largest group of cases was referred for post-operative treatment within two weeks after operation, but all within eight weeks. We believe that practically all cases can and should be referred for post-operative irradiation.

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TABLE IX

Average Time Intervening between Operation and Röntgen Treatment in Post-operative Group
(Average 4.21 weeks)

Treatment started	No. of cases
2 weeks.....	77
3 weeks.....	37
4 weeks.....	46
5 weeks.....	15
6 weeks.....	24
7 weeks.....	16
8 weeks.....	36
Total.....	251

tion within two weeks after operation. The object of this irradiation is to destroy any cancer cells that may have been left behind, either locally or in the neighboring lymphatics. We are quite sure that the earlier these cases are treated the better will be the results providing the treatment is adapted to the patient's general condition.

TABLE X

Classification of Types and Extent of Involvement in 977 Cases of Cancer of the Breast

	Cases	Per cent.
a. Pre-operative and post-operative cases.....	88	9
b. Post-operative.....	251	26
c. Recurrent with metastasis; involvement of bones, glands, or chest.	419	43
d. Primary inoperable cases.....	167	17
e. Primary operable.....	52	5
Total.....	977	100

It should be noted in Table X that nearly twice as many cases were sent on account of recurrences and metastases as for post-operative irradiation. We believe there will be very few recurrences, if patients are given skillful and thorough post-operative irradiation.

Of the 123 cases in which no microscopical section was obtained, forty-seven were recurrent and metastatic so that seventy-six or 7.7 per cent. of the total might have the diagnosis disputed, except on clinical evidence. Of these seventy-six cases, thirteen were primary operable, in which operation was refused or was inadvisable because of some physical condition, leaving sixty-three cases in which the surgeon's judgment must be accepted.

In 136 cases no biopsy was made because the disease was clearly malignant and inoperable.

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TABLE XI

Histological Classification

	Cases
None obtained (including primary operable—only 13 cases were clinically doubtful)	123
None made (inoperable primary and recurrent).....	136
"Carcinoma".....	224
"Malignant".....	129
"Fibroadenoma" (these cases were sent to us because of later recurrence and metastasis).....	18
Colloid carcinoma.....	2
Paget's disease.....	8
Adenocarcinoma.....	79
Medullary carcinoma.....	13
Scirrhus carcinoma.....	163
Carcinoma simplex.....	41
"Benign tumor" (sent to us later because of recurrence and metastasis).....	11
* Carcinoma en cuirasse.....	29
Papilliferous cyst carcinoma.....	1
Total.....	977

* The diagnosis submitted by the surgeon or pathologist.

Of the eighteen cases diagnosed as "fibroadenoma" at the time of the operation and all of which were sent to us because of recurrences or metastasis, nine died of carcinoma.

In the discussion of the 1925 paper, it was suggested that this group of "fibroadenomata" should be eliminated—because it was not understood that they were recurrent cases. A recurrence in our opinion is as good proof of malignancy as a microscopical diagnosis. The experiences with these latter twenty-nine cases ("fibroadenoma," eighteen, and "benign tumor," eleven) shows that one cannot always depend upon the microscopical report, due, of course, to the fact that the malignant portion of the tumor was not brought under the microscope.

The eleven cases diagnosed at the time of operation microscopically as "benign tumor" were sent to us on account of recurrences or metastasis, and of these, eight cases died of the disease.

TABLE XII

Classification of Types and Extent of Involvement in 977 Private Patients with Cancer of the Breast

The groups under each subdivision are classified after the fashion of the generally accepted surgical tables:

Group I.....	Early operable—no glands involved
Group II.....	Late operable with glands involved
Group III.....	Local recurrence—operable
Group IV.....	Local recurrence, inoperable, primary and secondary

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a. Cases receiving both pre-operative and post-operative treatment

Group	Before operation	After operation	No. of cases	Per cent.
A I	No glands.....	No glands.....	20	22
B II	Glands.....	No glands.....	37	43
C IV	No glands.....	Glands (not removable).....	19	21
D IV	Glands.....	Glands (not removable).....	12	14
Total.....			88	9*

b. Cases receiving post-operative treatment

E	I	No glands at operation, and no glands when radiation was begun	55	22
F	II	Glands at operation, but no glands when radiation was begun....	99	40
G	IV	Glands at operation, and glands when radiation was begun.....	72	29
H	IV	No glands at operation, glands when radiation was begun.....	25	9
Total.....			251	26*

c. Recurrent cases treated by radiation

I	III	Local recurrence.....	62	15
J	IV	Local recurrence in glands, axilla and supraclavicular region.....	67	16
K	IV	Local recurrence metastasis, mediastinum—lungs.....	30	7
L	IV	Local recurrence in axilla and supraclavicular and mediastinal regions.....	219	53
M	IV	Local lesion and metastasis to spine and other bones.....	14	3
N	IV	Metastasis, mediastinum, lungs and bones.....	27	6
Total.....			419	43*

d. Primary inoperable cases treated by radiation

O	IV	Fixed to skin or glands with axillary supraclavicular and mediastinal distribution	112	67
P	IV	Fixed to skin or glands with axillary, supraclavicular involvement plus bone metastasis	28	17
Q	IV	Made operable without chest metastasis	19	11
R	IV	Made operable with chest (palliative operation)	5	3
S	IV	Removed by electrocoagulation	3	2
Total			167	17*

e. Primary operable cases treated by radiation

V	I	Primary operable, unquestionably malignant (refused or physically not fit).....	39	75
T	I	Primary operable, questionably malignant, (3 per cent. of all cases).....	13	25
			<hr/>	<hr/>
		Total.....	52	5*

* Per cent. of 977 cases.

Referring to Table XIII, which is the general summary of all the work, it will be observed that in the *Pre-operative and Post-operative Group*, the three-year recoveries vary from 65 to 50 per cent. with a general average of

TABLE XIII

Statistical Study of Radiation Therapy in Carcinoma of the Breast (977 Cases) Duration of Life after the Beginning of Treatment—1902 to June, 1927, with Varying Technique

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59 per cent., and five-year recoveries vary from 62 to 12 per cent., with a general average of 50 per cent. This is less than the recoveries in the post-operative group, but it must be remembered that nearly all of these cases were advanced and doubtfully operable or totally "inoperable" before irradiation. Therefore, five-year recoveries of 50 per cent. is very good. Pre-operative irradiation is probably advisable in all but the strictly localized cases, but we advise pre-operative irradiation especially when there is skin ulceration or supraclavicular glands.

Post-operative irradiation is proven to be of very definite value, as is shown in this group in which the three-year recoveries vary from 96 per cent. to 37 per cent., depending upon the extent of the disease, giving a general average of 62 per cent. The five-year recoveries vary according to the extent of the disease from 87 per cent. to 30 per cent., but with a general average of 53½ per cent. In the group in which there was glandular involvement at the time of operation which are usually considered the late operable cases, 55 per cent. were well at the end of five years. This is about two and a half times as many recoveries as occur from operation alone, and should leave no doubt as to the advisability of post-operative irradiation in all cases of cancer of the breast.

We realize that these results differ from those reported by Harrington, in which his results seem to indicate that the irradiation added very little. We made inquiry concerning this and found that the more advanced cases were referred for post-operative treatment; that the radiation treatment in these early years was not well developed at the clinic; and finally, and most important, that as Harrington says, "In a large percentage of cases in which the Röntgen-ray was used initial treatment at the clinic and subsequent treatment elsewhere had been given." These factors, we believe, explain the marked difference in observations by Harrington and ourselves, for we attach great importance to a careful technic.

Recurrent and Metastatic Carcinoma forms the largest group, and these recurrences were recognized from two weeks to five years before being sent for treatment, but with an average of 6.6 months, some of which had from one to five operations for recurrences before the disease for which we irradiated; and nearly all had associated metastasis. With such material our three-year recoveries varied from 56 per cent. to 14 per cent., but with a general average of 39 per cent. The five-year recoveries varied from 47 per cent. to 4 per cent., but with a five-year recovery of 20 per cent. of all cases treated for recurrence and metastasis.

Primary Inoperable Carcinoma shows 167 cases treated with three-year recoveries of from 84 per cent. to 35 per cent. and with a general average of 43 per cent. The five-year recoveries vary from 58 to 25 per cent., but with a general average of 30½ per cent. of all cases treated. This is a better percentage of five-year recoveries in inoperable cases than from operation alone in the operable cases with axillary involvement.

The Primary Operable Group of Carcinoma of the breast, in which there

RÖNTGEN THERAPY OF BREAST CARCINOMA

TABLE XIV

Statistical Study of Radiation Therapy in Carcinoma of the Breast (726 Cases) Duration of Life after the Beginning of Treatment—1902 to 1922

During the Period before the Use of the High Voltage X-rays and the "Saturation Method" (Pahler)

[illegible]

TABLE XV
Statistical Study of Radiation Therapy in Carcinoma of the Breast (231 Cases) Duration of Life after the Beginning of Treatment—1922 to June 1, 1927
 During the Period of the Use of the High Voltage X-rays and the "Saturation Method" (Pfahler)

Other Details and Abbreviated Words Are Shown in Table XII																					
Group	Months alive												Total	Alive 3 years		Alive 5 years					
	6	8	1	1½	2	2½	3	3½	4	5	6	7		8	Number	%	Number	%			
<i>a. Cases receiving both pre-operative and post-operative irradiation (39 cases)</i>																					
A I	Op. no invol. of gl.	2	—	—	—	1	—	1	—	1	1	—	1	8	5 of 8	62	3 of 4	75			
B II	Op. with invol. of gl.	—	2	—	—	2	—	2	2	4	1	—	—	15	11 of 15	73	7 of 11	63			
C III	No gl. at op.—gl. after op.	—	—	2	—	1	—	—	—	2	—	2	—	8	4 of 8	50	2 of 4	50			
D IV	Gl. at op. and gl. after op.	1	—	1	—	1	—	3	—	1	—	—	1	8	5 of 8	62	1 of 5	20			
Total and average																	39	25 of 39	64	13 of 24	54
<i>b. Cases receiving post-operative irradiation (50 cases)</i>																					
E II	No gl. op.—no gl. when irradi.	—	—	—	—	1	—	4	—	4	6	5	—	3	23	22 of 23	95	14 of 15	93		
F II	Gl. op.—no gl. when irradi.	—	2	1	3	—	—	—	—	2	4	2	2	16	10 of 16	62	8 of 14	57			
G IV	Gl. op.—gl. when irradi.	1	1	—	2	—	—	2	—	1	1	3	—	9	6 of 11	54	3 of 4	75			
H IV	No gl. op.—gl. when irradi.	1	—	2	—	1	—	3	—	—	—	—	—	9	5 of 9	55	2 of 3	66			
Total and average																	50	43 of 50	73	27 of 36	75
<i>c. Recurrent cases treated by irradiation (88 cases)</i>																					
I III	Local recurrence	—	—	—	2	1	2	—	2	2	1	—	1	11	8 of 11	72	4 of 8	50			
J IV	Rec. gl. ax. and s. c.	2	1	2	1	1	—	4	—	1	1	—	—	14	7 of 14	50	2 of 9	22			
K IV	Rec. med. and lungs	2	2	2	2	—	—	—	—	1	—	—	—	11	3 of 11	27	1 of 10	10			
L IV	Rec. ax. and s. c. and med.	5	2	6	4	2	—	2	—	3	5	1	—	30	11 of 30	36	6 of 13	46			
M IV	Loc. les., met. spine and bones	—	2	1	2	1	—	1	—	—	2	—	—	8	3 of 8	37	2 of 5	40			
N IV	Met. med.—lungs and bones	4	—	2	2	2	1	1	—	1	1	—	—	14	3 of 14	21	1 of 11	9			
Total and average																	88	35 of 88	40	16 of 56	28½
<i>d. Primary inoperable cases treated by irradiation (48 cases)</i>																					
O IV	Fix. sk. or gl. and ax. s. c. and med.	7	—	6	1	3	—	1	—	2	—	2	1	25	8 of 25	32	5 of 21	23			
P IV	Fix. sk. or gl. and ax. s. c. and b. met.	2	—	—	1	3	—	2	—	4	2	2	—	16	10 of 16	62	4 of 9	44			
Q IV	Made op. without chest met.	—	—	—	—	—	—	—	—	1	1	—	—	5	4 of 5	80	2 of 3	66			
R IV	Made op. with chest (pall. op.)	1	—	—	—	—	—	—	—	—	—	—	—	1	0 of 1	0	0 of 1	0			
S IV	Remov. by electrocoagulation	—	—	—	—	—	—	1	—	—	—	—	—	1	1 of 1	100	0 of 1	0			
Total and average																	48	23 of 48	48	11 of 35	32
<i>e. Primary operable cases treated by irradiation (17 cases)</i>																					
V I	Prim. op. unques. malign. (refused or phys. not fit)	—	—	—	—	—	1	—	—	6	2	4	2	—	15	14 of 15	93	8 of 10	80		
T I	Prim. op. questionable malign. (3 per cent. of all cases)	—	—	—	—	—	—	—	—	—	—	1	—	2	2 of 2	100	2 of 2	100			
Total and average																	17	16 of 17	94	10 of 12	83
Grand total and average																	251	142 of 251	56	77 of 163	47

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was no doubt about the clinical diagnosis, numbered only thirty-nine cases. These either refused operation or were physically unfit. Of these, there were 89 per cent. of three-year recoveries and 85 per cent. of five-year recoveries.

Total Values.—We have tried to classify the cases in a manner in which one could make a fair comparison, but it may be of value to summarize the entire group as cancer material and estimate in this manner the chances of recovery that a private patient has had in the past twenty-five years by a combination of surgery and irradiation. Taking, therefore, the whole material of 977 cases, there has been a recovery of 50 per cent. for a period of three years and 36 per cent. for a period of five years. This gives a far less gloomy picture of the results of the treatment of carcinoma of the breast than is usually presented, but, if all the knowledge which is now available is properly utilized, this percentage should be doubled, at least for private cases in which one gets better coöperation than is obtained in the hospital clinic case. The difference in the number of cases under treatment in the five years as compared with the three-year column is due to the fact that some of these cases were not referred more than three or four years ago.

Having made a general analysis of the radiation value in carcinoma of the breast during a period of twenty-five years, it seemed important to determine whether the statistics would justify our clinical opinion of definite improvement in our results since we have been using the high voltage rays and the "saturation method" combined as compared with the results obtained previously. Table XIV shows the results obtained during the twenty years preceding this technic, and during which time all improvements in radiology were also utilized as they were developed. We have, therefore, also classified the cases treated since 1922 by this later technic and apparatus, as is shown in Table XV.

TABLE XVI
*Comparative Results before 1922 (Low Voltage) and
after 1922 (High Voltage and "Saturation")*

Group	1902 to 1922 Low voltage— variable technic		1922 to 1927 High voltage and "saturation"	
	3 years Per cent.	5 years Per cent.	3 years Per cent.	5 years Per cent.
Pre-operative and post-operative—all classes	55	47	64	54
Post-operative with no ax. glands	96	84	95	93
Post-operative with ax. glands	63	55	62	57
Post-operative—all classes	59	49	73	75
Recurrent and metastatic—all classes	39	19	40	28½
Primary inoperable—all classes	42	30	48	32
Primary operable—clinically positive	87	87	93	80
Average results in all cases treated	48	33	56	47

Table XVI shows a very definite improvement in all classes as a result of our improvement in apparatus and technic. It shows further that with

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both pre-operative and post-operative treatment according to modern technic even when many cases were inoperable, 54 per cent. showed five-year recovery.

It shows further that a patient who goes to the surgeon before the axillary glands are involved has a 93 per cent. chance of five-year recovery, providing she gets thorough and skillful post-operative irradiation, and if there are axillary glands there is still a chance of 57 per cent. with our most modern methods.

The *Recurrent and Metastatic* cases still show a 28½ per cent. salvage after five years.

The *Primary Inoperable* case need not be abandoned as hopeless when there is a 32 per cent. five-year salvage.

With regard to the *Primary Operable* cases, we recommend operation when this is practical as the shortest and most certain way out of trouble, but when this is not practical, we may still expect an 80 per cent. recovery from thorough and skillful irradiation.

A very striking demonstration of progress is shown in the last line of Table XVI, in which the general results in all classes of cases of carcinoma of the breast treated between 1902 to 1922 are compared with those treated from 1922 to 1927. The latter group was treated by the more modern technic which shows 47 per cent. of five-year recoveries as compared with a general average of 33 per cent. before 1922. It is also most encouraging that a case of cancer of the breast in the general average today has a 47 per cent. chance of cure.

TABLE XVII

Statistical Study in Twelve Cases of Carcinoma of the Breast in Males

No. of cases	Age	Duration of tumor	Operation	Metastasis	Recurrence before rad.	Alive	Dead
I	55	5½ years	5 years before rad.	To rt. ax., s. clav. reg.	1 year	1 year	Yes
II	68	1 year	2 months before rad.	To rt. and lt. axilla	4 weeks	1 year	Yes
III	78	9 months	3 weeks before rad.	To lt. ax., s. clav. reg.	None	1 year	Yes
IV	55	2 weeks	6 days before rad.	None	None	2 years, 11 months	Yes
V	60	3 years	1 year before rad.	To rt. ax. and chest	5 months	1 year	Yes
VI	32	2 months	4 weeks	None	None	7 years	No
VII	60	3½ years	3 years before rad.	To rt. ax., s. clav. reg.	2 years	11 years	No
VIII	74	8½ years	8 years before rad.	To rt. ax.	1 year	3 years	Yes—myocarditis
IX	65	4 weeks	2 weeks before rad.	None	None	6 years	No
X	73	4 weeks	Pre- and post-op. tr. 2 wks.	To rt. ax.	None	5 years	Yes—apoplexy
XI	60	1½ years	1 year before rad.	To rt. ax., s. clav. reg.	5 months	9 months	Yes
XII	50	6 months	X-ray treat. electrocoag. X-ray treat. after dest.	To rt. ax., s. clav. reg.	None	8 years	Yes—cardiac disease

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Carcinoma of the Breast in Males.—Judd and Morse have recently reviewed the former reports and have added seventeen cases of carcinoma of the breast in males. In general, a little more than 1 per cent. of carcinomata of the breast occurs in males. We have twelve cases in this series, and have not noticed any appreciable difference in our results as compared with carcinoma in the female. Judd and Morse believe that they are more malignant and have not found the röntgenological treatment of appreciable value. We have seen recurrences and metastasis disappear under irradiation. Table XVII shows definite value in irradiation.

Nine of these cases were proven carcinoma by microscopical examination. In the remaining three cases, none was obtained, but they all died within one year of carcinoma.

Of the twelve cases, six were recurrent, four post-operative, and one received pre- and post-operative treatment, one was primary, with a protruding growth beyond the skin (No. XII), this part was removed by electrocoagulation, but not the whole breast.

Case No. IV developed a recurrence in the axilla two years after operation and irradiation, which yielded to further irradiation, but a fibrous nodule remained. He consulted a surgeon in a distant city who urged immediate operation, which was done by him on the succeeding day and two days later he died.

Six cases lived three years—50 per cent.

Five cases lived five years and over—41 per cent.

Three cases are living at present—25 per cent., six, seven, and eleven years respectively.

SUMMARY

The review of 977 cases treated during a period of twenty-five years shows:

1.—*Pre-operative and post-operative irradiation* will render many inoperable and doubtfully operable cases operable.

2.—*Post-operative irradiation* gives a general average of all cases of 53½ per cent. five-year recoveries, and with the more modern technic this is increased to 75 per cent. In the operable group, in which the disease had extended only to the axillary glands, there were 55 per cent. of five-year recoveries, and with the more modern technic 57 per cent. after five years.

3.—*Recurrent and metastatic carcinoma* gave a general average of 20 per cent. of five-year recoveries and 28½ per cent. when only those treated by the modern methods are considered.

4.—*Primary inoperable carcinoma* gave 30½ per cent. of five-year recoveries, which shows that if a patient cannot be operated upon there is still considerable hope from thorough irradiation.

5.—Only thirty-nine cases of primary operable carcinoma of the breast were treated. These were undoubted clinical carcinoma but unfit for operation or refused operation, but these showed 85 per cent. of five-year recoveries. We recommend operation in all operable cases, to be followed by irradiation.

RESULTS OBTAINED WITH CARCINOMA UTERI TREATED BY RÖNTGEN-RAYS FROM 1915-1925

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FROM THE ERLANGEN RÖNTGEN INSTITUTE

IN THIS Ewing Cancer Tribute, I have thought it opportune to publish the results and the conclusions thereof in the care of those patients who had been treated during the years 1915-1925 for cancer of the uterus.

The treatment consisted, in this decade, chiefly in Röntgen therapy; only in special cases were small quantities of radium energy given in addition. This was done when the dose necessary for the destruction of cancerous tissue could be brought only with great difficulty to the site of the tumor.

For the statistics under discussion, this was the case with cancer of the corpus uteri and with those tumors of the cervix which, on account of a descensus uteri, have slipped into the vagina, so that the central ray of a field of incidence applied to the suprasymphyseal region can scarcely reach the tumor. It was only in the second half of this decade that I used systematically an additional radium dose with cancer of the corpus uteri, while, during the first half, also with this form of cancer, Röntgen therapy alone was employed.

I. For this decade the technic of irradiation was, on principle, the same, though, since 1920, due to important improvements of the apparatus, the time of irradiation became much shorter.

The dose applied, the "cancer dose," is 110 per cent. of the HED, *i.e.*, Hauteinheitdosis, or unit skin dose (USD).

The value of the USD in its original definition can be expressed by the standardized international r units; thus, a value of about 600 r is obtained. But it is to be taken into consideration that this value is valid only if the dose is applied at one or two sittings in the course of forty-eight hours. Suppose the dose is distributed over a long time, the same amount of r units would actually produce a smaller biological effect, for it has been known a long time that distributing a dose over some period means a diminution of biological action. The reason for this lies in the recuperative faculty of the cells being able to compensate the action of small Röntgen-ray quantities. The lowest limit of irreparable injuries of the cancer cell lies with 60 per cent. of USD = 360 r .

This is why I think it necessary with cancer therapy to apply the dose wanted for destruction of cancer, if possible, at one sitting, or at least in the course of forty-eight hours. Only in this way is it possible to load the surrounding tissue with the least possible quantity of rays. During the past years experiments have been made over and over again with the purpose of distributing the Röntgen quantities over a series of days. It resulted

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from these experiments with certainty that the total dose to be applied to a tumor must be much greater than the total doses administered by means of my technic, if a success shall be guaranteed.

With regard to the technic, it would be the same whether the irradiation at one sitting or the distribution over a long time is used, if only the loading of healthy tissue with Röntgen-rays would be the same in both cases. But this is noways the case, as we have seen.

It is certain, without further argumentation, that the recuperative faculty of the cancer cell whose characteristic is rapid growth must be different from that of normal body cells distinguished by normal slow metabolism.

We know from a series of fundamental experiments that cells having slow metabolism, cumulate Röntgen-rays in a much stronger degree, or, to put it in a different way, those cells take a much longer time than cancer cells to compensate small Röntgen injuries.

Therefore, with the method of fractioned doses, the organism is only apparently more spared than with the other one; actually, the healthy tissue will cumulate the rays in a much higher degree than the cancer cells. The final destruction of cancer cells thus is paid for by much greater injury of healthy tissue. Clinical experience has proved this incontestably. If the treatment is given with fractioned doses, induration is seen sooner and in a more pronounced degree than with the treatment at one sitting. All this justifies my holding fast to the principle of applying the dose at one sitting.

As to the technic of irradiation, we proceed in the following way: At first, the primary tumor is irradiated by concentrating Röntgen-rays onto it from a series of fields of incidence of the size of six by eight centimetres. The technic being often described,* may be supposed to be known. Eight weeks later, the parametria are treated. In the period with which these statistics deal, there is also a difference in so far as, prior to 1920, the treatment of parametria was divided in two sittings, first one side being irradiated, and, after six to eight weeks, the second one.

Since 1920 (up to the present time) both parametria are irradiated at one sitting in the course of forty-eight hours.

II. The principles according to which my statistics are drawn up are the following:

All positive cases of cancer received for treatment at the clinic are followed up in the statistics whether the treatment could be finished or not. They are considered to be "cured" only when, five years after the treatment is finished, the patients are free of symptoms and able to work according to their age.

There are two groups: *symptom-free* (healthy) cases and *lost* ones.

Under the heading of "lost cases" are included:

(a) All those who have died whether of carcinoma or of an intercurrent disease, even if at autopsy all cancerous growth had disappeared; and

* Radiology, vol. v, p. 500.

(b) Those cases who showed local or metastatic cancer or whose general health implied the existence of latent metastases.

Besides, the material is grouped in *operable* and *inoperable* cases. Those are considered to be operable whose cancerous growth is still restricted to its primary site; inoperable, those with affected lymphatic glands or with symptoms of general dissemination. According to the strict statistical principles drawn up by Winter, cases hopeless from the beginning are also included.

Recurrences after operation form a separate group.

Stress must be laid on the fact that all cases are followed up. Those very few (four) which could not be traced, because they had moved abroad, are counted as dead.

The statistics of cancer of the uterus of the Erlangen Röntgen Institute for the decade of 1915-1925 covering over 956 patients, yield the following results:

(a) *Cancer of Cervix Uteri*

(1) Operable cases.— $125:75 = 60$ per cent. symptom-free and able to work according to their age.

(2) Inoperable cases.— $712:86 = 12$ per cent. symptom-free and able to work according to their age.

(b) *Adeno-carcinoma of Corpus Uteri*

(1) Operable cases.— $59:41 = 69.5$ per cent. symptom-free and able to work according to their age.

(2) Inoperable cases.— $160:5 = 8.3$ per cent. symptom-free and able to work according to their age.

The importance of these statistics lies in the fact that a considerable number of patients (956) were treated with nearly the same technic in the course of ten years, while the statistics of many other institutes are dealing with frequently changing methods.

Of course, the technic became more and more improved every year, but the principle drawn up in 1915 of applying the cancer dose, if possible, at one sitting or in the course of forty-eight hours, was followed ever since. Improvements were made especially with regard to electrical conditions, with the result that the time a treatment took became much shorter in a later period (1922-1925) than it was in the first one (1915-1919), as mentioned before.

As the most essential improvement of the second half of this decade dealt with in the statistics is to be considered the fore- and after-treatment,* not less important in the sense of auxiliary therapy is *copper treatment*.

The value of these improvements is clearly shown by partial statistics which are won under the same conditions as the total one and deal with the years 1922-1925. For this period, the following percentages are obtained five years after treatment was finished:

Operable Cases

Cancer of cervix uteri, 66.6 per cent.

Cancer of corpus uteri, 80 per cent.

* Radiology, vol. i, p. 74.

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Inoperable Cases

Cancer of cervix uteri, 15 per cent.

Cancer of corpus uteri, 14 per cent.

A short description of the *technic of coppering* may follow: The idea which led to the elaboration of this technic was to produce secondary radiation in the tissue by metallic particles introduced by means of iontophoresis.

For cancer of cervix uteri the technic is the following: As anode a copper tube is used which is shaped in the form of the rose of a watering-can. The copper tube is uncovered for about three to five centimetres of its length, the remainder being protected by hard rubber. It is wrapped in cotton wool and gauze in order to form a kind of sponge electrode, which, on introduction to the vagina, fits closely to the mucous membrane. If the vagina is not sufficiently plugged in this way, small burns of the mucosa may result (Joule's heat). The portion of the rubber tube which lies outside the vagina is armed with a pinch-cock and is connected with a douche can which supplies a solution of cuprum selenicum (5 in very small doses—about 15–20 drops per minute.) Care must be taken that the whole plugging is sufficiently moist, and that, at the same time, no liquid escapes from the vagina. The hollow cathode, consisting of clay, is filled with a solution of rock salt; the size of this electrode which is put on the abdomen is about 300–400 square centimetres. Good contact with the skin is essential. The current is applied from an accumulator of 8 volts. A resistance is inserted in the electric circuit, permitting the regulation of the tension; the intensity is read from a milliamperemeter.

In order to regulate the circuit of the current from the vaginal anode to the cathode, a careful insulation of the skin is to be observed by putting a broad layer of grease over the symphysis and round about the cathode. If insulation and connection are correct, only a weak current is passing, when joined up; the pointer of the milliamperemeter rises slowly. The normal average intensity amounts to about 40–50 milliamperes. Experience has shown that the use of from 200–250 milliamperè-hours is most suitable. When 300 milliamperè-hours are surpassed, injuries may occur. We have never seen injuries up to 250 milliamperes, nor even irritation of kidneys, in spite of the fact that copper may be found in urine, or even in saliva, about two days after copper treatment.

Copper treatment is administered to all cases of cancer of cervix uteri; eventually, also, to cases of cancer of corpus uteri, as well as with all other ulcerated cancers.

The physical action of coppering consists in iontophoresis and electrolysis. Thus, the tissue lying between cathode and anode is imbibed with copper salt solution, most strongly in the neighborhood of the cathode. Besides, copper ions are transported by means of electrolysis in the direction of the cathode. As we may presume that the walls of cells do not offer any resistance to the copper ions, copper particles are supposed to enter the cells. Near the anode, selenic acid is being liberated so that an irritative action is produced in the superficial layers.

With regard to being an auxiliary to Röntgen therapy, secondary radiation produced by copper ions is of minor importance only. According to measurements, the local increase of the so-treated tissue in susceptibility to Röntgen-rays is about 20 per cent. at the utmost. Nor can the oligodynamic action of copper be of particular consequence, but the clinical value, consisting principally in a *disinfecting action* in the sense of *deep disinfection*

tion, and becoming evident in accelerated regression of the tumor as well as in more rapid healing up (cicatrization and formation of normal tissue), is of prime importance.

In one of my former papers,* I have pointed out that the infection of a tumor cannot be taken too seriously. At the Radium Institute in Paris the same statement has been made, *i.e.*, that infected cancerous growths have much worse chances to be healed than non-infected ones. Further investigations have shown that radiosensitiveness of a cancer cell is diminished while that of the surrounding tissue is increased. Thus, radiosensitiveness of healthy and diseased tissue becomes nearly the same. It results, hereof, that susceptibility reduced by infection cannot be compensated by augmenting the dose, for healthy tissue, extremely sensitized by infection, will answer with serious injury. Our clinical investigations correspond with those published by Lacassagne, from the Radium Institute of Paris. The importance of the problem follows from the proposition of this author first to perform a deep disinfection with infected tumors before beginning the treatment, though there is no doubt that precious time is lost during disinfecting treatment.

As I have already shown, we are well entitled to see in copper treatment an especially favorable method of deep disinfection. It is from this reason that the action of coppering is so propitious with infected tumors.

To ascertain the value of copper treatment by drawing up statistics is not easy; even if one tries to compare as many homogeneous cases as possible, it might be objected that, judging from the local findings and the general health of the patient, it is impossible to foretell which turn the disease will take. Besides, it would be necessary to subdue all patients to exactly the same conditions of treatment, in order to be able to pass an incontestable opinion on the action of copper treatment. But, being convinced of its value, I cannot make up my mind to exclude patients from this therapy for experiment's sake. I, therefore, have for this comparison only those cases at my disposal which have been treated with Röntgen-rays before copper treatment was inaugurated and a second group from a later period treated by copper iontophoresis. In the course of time, though I have not changed the principles of my method, the deep action of radiation and the time of application have been altered by technical improvements. Even the general conditions of life are not the same with these patients. That is why I can render my results only with certain reservations though I have chosen patients whom I have personally examined.

I contrast two groups, each of sixty cases of cancer of cervix uteri (squamous-cell carcinoma), whose clinical findings could be characterized as inoperable, but still localized to the pelvis: infiltration of both parametria, in all cases streptococcus hæmolyticus positive.

The percentage of cure is:

* Acta Radiologica, vol. vii, p. 675.

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Three Years After the Treatment Is Finished

Group I (without copper treatment), 8 per cent.

Group II (with copper treatment), 16 per cent.

Five Years After the Treatment Is Finished

Group I (without copper treatment), 6.3 per cent.

Group II (with copper treatment), 13 per cent.

There is certainly an evident difference, but these statistics must by no means be overvalued, as clinical homogeneousness is difficult to judge. As to infiltration of parametria, for instance, nobody can decide, with certainty, whether this infiltration is cancerous or only inflammatory. According to my experiences, this difference with regard to the chance of a cure is not essential with exclusive radiotherapy as any inflammatory process means a great complication for this therapy. If, however, Röntgen therapy is combined with an efficient disinfecting treatment, the results obtained with inflammatory infiltration will be much better than with cancerous infiltration. But, anyhow, the value of any therapeutic method is ascertained by definite cures.

III. Repeatedly, I have, with regard to radiotherapy, pointed out the importance of life conditions and of systematic after-care. In 1923, I could report statistical results* with cases well followed up, having the same clinical findings. The difference which became manifest in the results obtained with two groups I had formed, was produced by the condition of life under which these patients lived after having had Röntgen therapy. With one group of patients all that could be done was to hospitalize them for a long time or to send them to a sanatorium for completion of cure. Others, again, had all they wanted as to rest, diet and nursing at their homes. When it was impossible to give them the benefit of long hospitalization, these women had to return to their jobs in poor or even miserable home conditions after the treatment was finished and when they were just beginning to recover. At that time (1923) we stated, three years after treatment was finished, a difference of results from 42 : 22 per cent. and four years afterwards from 41 : 15 per cent.

With cases I recently have controlled personally with regard to this problem, the difference was no longer so marked as with the material followed up in 1923, when the conditions of life in Germany were still affected by war and inflation times. But the results won with a series of 140 patients having the same clinical findings show, nevertheless, the following difference four years after the treatment was finished:

Group I (good conditions of life), 46 per cent. symptom-free and able to work.

Group II (bad conditions of life), 32 per cent. symptom-free and able to work.

All the same, these results are very important and have led me to insist on good after-care. As conditions of life have become better these last

* Strahlentherapie, Bd. xv, p. 770.

years, the benefit of hospitalizing patients for some weeks can be conferred to a broader mass of patients than before. After-care, as I have pointed out elsewhere,[†] must aid the body to eliminate the products of degeneration. Mechanical cleaning is obtained by disinfecting irrigations; resorption from the vagina, not being of much importance, plays a rôle anyhow. For those masses of decayed cells which have been swept off by the blood-stream, something can be done by medication with the purpose of accelerating metabolism. Sulphur administered either *per os* or by means of intravenous injections has proved to be very successful. Arsenical preparations, formerly greatly appreciated with cancer therapy, are of essential importance only with patients in poor systemic condition. With women who tend to grow stout, arsenical medication is not wise. Change of altitude has proved to have a very favorable action, the influence of altitude, which has an accelerating effect on metabolism, being particularly propitious for the elimination of degeneration products. It is of prime importance to watch the weight curve after radiation therapy. Loss of weight, when conditions of life are otherwise satisfactory, is a bad symptom.

IV. Though statistics demonstrate clearly the value of special care after treatment for cancer, it is very unsatisfactory that one knows so little about the relations of systemic conditions and cancer. That is the reason why any procedure to cure the body of the cancerous disease offers so little chance of success. The disappointments one experiences over and over again with initial cancerous growths prove this above all.

The reason for this limit of our efficiency lies partly in early dissemination of cancer from ever so small a primary tumor. I recently was able to state by autopsy in six cases that the cancerous growth in the corpus uteri and in its surroundings was completely healed up, but that those patients had died of distant metastases.

Thus, the size of a cancerous growth, in as far as the tumor may be characterized as being localized, does not permit one to draw any definite conclusion as to prognosis, though, in general, it is correct to presume that the bigger the primary tumor, the worse the prognosis.

Neither are systemic condition nor looks of the patient determinant with regard to the final result of treatment. Every one knows those patients who, seemingly in blooming health, come with an initial cancer of uterus for treatment, but die in the course of one to two years, while others of apparently cachectic condition, a definite cure is obtained.

I have drawn up some statistics of cancer of the cervix uteri dealing with the fate of young women (operable cases). It yields, five years after the treatment is finished, the following results:

Group I (1916-1921), symptom-free and able to work, 38 per cent., instead of 56 per cent. of the total average.

Group II (1922-1925), symptom-free and able to work, 50 per cent., instead of 66 per cent. of the total average.

[†] Radiology, vol. i, p. 74.

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These results fall considerably short of the standard. That they cannot be explained by chance is shown by the great surgical statistics. Here, also, cancerous growth with young women has a much more grave prognosis *quoad sanationem* than with women over forty years of age. The reasons for this are unknown: another example for the fact that the relations between destruction of cancer and collaboration of the total organism to obtain a definite cure, still offer a wide field of study.

V. The efficiency of any radiotherapeutic method becomes manifest after surgical operation. In the subsequent statistics I have assembled all those cases of cancer of uterus on which a Wertheim operation had been performed at some time or other, and which came with recurrence for Röntgen treatment. The clinical quality of these cases differs widely, so that really a series of subdivisions would be necessary. But to be loyal to the principle of the all-comprising statistics of Winter, all those cases are included which are hopeless from the beginning, though they are a burden especially for this statistics table.

Results Obtained with Recurrences After Operation for Cancer of the Uterus by Röntgen Therapy

118 patients, three to four years after treatment symptom-free and able to work
20 = 17 per cent.

104 patients, five to six years after treatment symptom-free and able to work
10 = 9, 6 per cent.

59 patients, eight to nine years after treatment symptom-free and able to work
4 = 6, 7 per cent.

VI. I cannot close the discussion of my statistics without referring to a special circumstance. The percentages of cure, obtained for localized cancerous growth of the uterus, already attain a considerable height today; the more desolate, on the contrary, are the results with the so-called inoperable cases. Though we may be satisfied in thinking that without radiation therapy these cases would all be lost, a cure percentage of 12 per cent. is still unsatisfactory. Although, with our methods of treatment, we expect to improve the results from year to year, still only a small per cent. can be added.

From the total statistics of those cases of inoperable cancer where the cancerous growth had extended over the pelvis without having formed distant metastases—a cure percentage of 22 is obtained. This seems to be the best result possible. The difference between operable and inoperable cases remains great. This fact proves clearly that besides further improving our *methods* of cancer therapy we must try to reach cancer cases earlier. Thus, the demand of the years to come will be: *Wider information among mankind as to early symptoms of cancer and the possibility of curing an initial cancerous growth.*

In this propaganda to fight cancer, the United States of America takes the lead in an aggressive way.

THE TREATMENT OF CANCER OF THE BODY OF THE UTERUS BY RADIATION

By CURTIS F. BURNAM, M.D.

OF BALTIMORE, MD.

FROM THE HOWARD A. KELLY HOSPITAL

CANCER of the body of the uterus is, with very rare exception, an adenocarcinoma and tends to metastasize somewhat more slowly than that of the cervix. Visceral and distant metastases are, however, much commoner than in the epidermoid carcinoma of the cervix. The disease is rare when compared to cervical cancer. The ratio between these two groups in our records is as one to fourteen.

Old age is a predisposing cause. Patients with uterine body cancers are much older on the average than those afflicted with the cervical, ovarian, and other gynæcological carcinomas. In 165 patients of this group, treated in the clinic of the Howard A. Kelly Hospital, the average age was fifty-seven years. This age probably is some years beyond the average age of all women with this particular form of cancer, because most of the patients were sent to us for radiation because of some physical disability—not infrequently old age itself. In the early cases, the average age was fifty-nine years; in the advanced cases, fifty-eight years; in the recurrent cases, fifty-one years; in the metastatic cases, fifty and a half years. The oldest woman in the group was eighty and the youngest twenty-eight years. Dr. Leda J. Stacy, in 333 cases treated at the Mayo Clinic, notes that it is fairly frequent in younger women—10.51 per cent. of her cases were under forty-five years of age. In our series, there were nineteen cases under forty-five years of age, exactly 11.5 per cent.

Heredity probably is an important predisposing cause but it is rather difficult to prove this on clinical material. There is a distinct tendency, with these patients, to develop cancer in some other part of the body of an entirely different type; and, occasionally, two distinct cancers are found at the same time in the same patient. As to the influence of race on the frequency of this cancer. There is a large negro population in Baltimore and, in our clinic, we see a great deal of cancer in the negro. It, therefore, is somewhat surprising to find only two negroes in the entire group of 165 cases. It is our impression that cervix cancer is relatively much more frequent in the negro than in the Caucasian and that it can be attributed to the prevalence among the negroes of the venereal diseases and, also, to the average greater number of pregnancies and poorer obstetrical care at labor.

In the literature, there are current and frequently repeated statements that cancer of the uterus is much more frequent in women with fibroid tumors, in those suffering from sterility, and in those who are unmarried. Without accurate information as to the percentage of fibroids in all women, of sterility in all married women, and of spinsterhood in general, our small

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group of cases is of limited value in throwing light on the importance of these factors. However, my impression is that they have little, if any, etiological significance. As only a small percentage of our cases was subjected to surgical operation, the determination of fibroids had to be made by clinical examination—a somewhat uncertain method. In the entire group, fibroids definitely were found only in 12 per cent. Doctor Stacy, in 269 operated cases, found 33.45 per cent. fibroids. C. C. Norris and Vogt in 115 cases, observed this complication in 21 per cent. James Ewing quotes Klob to the effect that 50 per cent. of all women over fifty have uterine fibroids; and that 20 per cent. of all over thirty-five are similarly affected. Uterine fibromata are much commoner in negroes than in whites but, apparently, body cancers are much rarer, and the reverse should be the case if fibroids cause or favor cancer.

Sterility does seem to be a predisposing, or, at least, an associated condition. In 127 records, where this question is clearly taken up, there were fifty-eight women who had children and sixty-nine who had none. In these women, there was, therefore, a 55 per cent. sterility. All of them had been married for years. Most of those who had children were multipara; the greatest number of children in any one case was sixteen.

Out of the entire group, twenty-six were married, 15.7 per cent. This does not seem a high percentage of unmarried women, but it may be, if only unmarried women of the age of our patients are considered.

Whenever the diagnosis of cancer of the body is established and the local conditions in the pelvis determined, there remains the obligation to examine the patient exhaustively for abdominal and general metastases. This is much more urgent than in cervical cancer.

Treatment.—It is convenient in considering treatment to divide the cases into the early operable, the late border-line and inoperable, the recurrent after operation, and the metastatic.

When the disease is limited to the uterus, there are two possible methods of successful treatment. Hysterectomy, long in use, is accompanied by a lower mortality and a higher percentage of permanent cures than the same procedure has yielded in treating cancer of the cervix. Recently, Stacy, Heyman, Schreiner, and others have reported methods and results in treating these early cases with radium alone. These reports point to the possibilities of the non-operative methods and Heyman, in particular, records a five-year cure rate comparable with that obtained by surgical operation. He, nevertheless, still feels that, unless there is some general contra-indication, such as old age and corpulence, very high blood-pressure, organic heart disease, nephritis, or diabetes, operation is the method of choice.

When the disease has extended beyond the uterus, there is very little field for operative interference, but there is still definite hope of a cure by radiation. We have had two patients who belong in the inoperable extensive group where a combination of operation and radiation has been of value. In one, in addition to a very large carcinoma of the body of the uterus, there was bilateral involvement of both ovaries. The patient was

in rather poor general condition and, at operation, the ovarian carcinomas were found densely adherent to surrounding structures. A rapid removal of both ovarian masses was carried out and, in place of removing the uterus, radium treatment was given to take care of that part of the disease. During the convalescence, additional radium radiation was given by crossfire method to the entire pelvis. The uterus, originally the size of a three and a half months' pregnancy, is now quite small and free of disease. The patient also seems quite well after two years. The second patient had a small, freely movable uterus which was removed along with the tubes and ovaries by abdominal operation, but a packet of glands was found over the iliac vessels—one of these was removed and found to be cancerous. After recovery from the operation, a systematic and careful radiation of the involved iliac region was carried out and this patient—now five years later—seems free of cancer. Such cases as these must be the great exceptions and the shock and lowered resistance from operations, in most of the inoperable cases, would only lessen the chances of benefiting by radiation.

When the disease has extended by metastasis beyond the first regional glands, operation obviously is contra-indicated. Exactly the same treatment holds true of all cases which have recurred after surgical removal of the uterus.

Operative Technic.—It does not fall within the scope of this paper to discuss the details of surgical treatment of cancer of the body of the uterus. There is a lower primary mortality from vaginal hysterectomy than from abdominal hysterectomy. The former method, however, in addition to yielding a smaller percentage of permanent cures, has the disadvantage of being applicable only to those cases where the pelvis is roomy, the uterus small and perfectly movable. The abdominal operation always should include removal of the tubes, ovaries, cervix and top of the vagina. There is a very definite primary mortality associated with abdominal panhysterectomy for corpus carcinoma. In our own series of twenty-seven cases where abdominal hysterectomy was resorted to, the primary death rate was 9 per cent. So far as general examination showed, these cases all were in good condition and were good operative risks. Doctor Stacy in a series of 239 cases from the Mayo Clinic reports a primary mortality of six per cent. The reports from the literature indicate a primary mortality running from about 6 per cent. to 15 per cent.

Technic of Radiation.—In the early cases, and in all cases so far as the disease of the uterine body is concerned, our chief reliance has been on intra-uterine radium treatment. There has been no primary mortality or serious complications.

Our source of radiation has been radon in a glass tube or bulb, surrounded by a millimetre of brass and three millimetres of rubber. We usually employ from one curie to three curies of radon, divided into from four to six equal parts. The tubes, to which strings are attached, are introduced into the uterine cavity and a dosage of from two and one half to three gram hours

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is given. The dosage is not surpassed unless the uterus is a very large one and the cavity very extensive. Crossfire radiation, either by radium or by X-ray, should be given with great care and mainly to the iliac glands and lateral walls of the pelvis. There is real danger of intestinal injuries if this radiation is super-added to the uterine radiation by central exposure. In the very large, inoperable cases, and in the metastatic cases, the conditions are so variable that no definite plan can be laid out to cover groups of cases. Each patient must be individualized and the method decided upon which promises the most complete treatment. A great deal of this treatment is by crossfire radiation from the surface of the body. Unless several grams of radium are available, it is preferable to use X-ray. Where the radium is available, it is decidedly more efficacious.

The radiation of post-operative cases demands special consideration. Very frequently the small intestine has become adherent to the vaginal scar and the radiation which is given directly to the vault of the vagina should be of a very mild character. The lower vaginal wall, which is a frequent point of metastasis, can be treated more vigorously. The regional gland regions should be treated by crossfiring, as already has been referred to above.

Intra-uterine treatment is usually given under nitrous oxide anæsthesia, with the usual antiseptic precautions for intra-uterine handling. The patient is kept in the hospital for a few days until it is evident that complications will not take place. The discharge usually ceases within five or six weeks. Some of the larger uteri decrease as markedly as do fibroid uteri after radiation. After from ten to twelve weeks, the patient is brought back to the clinic, given a second anæsthesia, and thoroughly curetted. If no malignancy is found, no further treatment is given. If cancer still is present, either a hysterectomy or a repetition of the treatment is carried out. The former method is preferable unless the general condition contra-indicates any operative procedure.

The patients should be put in full possession of the facts as to their conditions and instructed to keep in touch with the clinic and report back at stated intervals, even when there are no symptoms.

Results.—It is not a simple matter to secure from the literature accurate data as to the percentage of permanent cures of cancer of the body of the uterus. Our own material from the operative standpoint is quite small. Heyman collecting from a number of reports notes 323 operations with 58.8 per cent. of cure. By radium alone, in fifty-two cases, there was 50 per cent. of five-year cure at the Radiumhemmet in Stockholm. John G. Clark reports 42 per cent. of three-year cures. Norris and Vogt, 44 per cent. cures. Stacy reports 269 cases treated by hysterectomy of whom she was able to trace 215. Of these, 108—50.2 per cent.—were living at the end of four years. A little more than 40 per cent. could be tabulated as living if all the cases unheard from were dead. However, sixteen patients who died subsequent to the operation died of other causes than cancer and this, of course, would raise the operable cure rate. Out of thirty-two patients treated by

radium alone, she was able to trace twenty-five, all but two of whom had died from the disease.

Our own cases are grouped under four headings: first, comparatively early, possibly operative cases; second, advanced inoperable cases; third, recurrent cases; fourth, cases already presenting metastases.

Comparatively Early, Possibly Operative Cases.—In this group, the cases should be subdivided into those treated by operation alone, by radium alone, by radium and operation, and by operation and radium. It has been our impression up until quite recently that if a patient were in normal general physical condition and the uterus freely movable, operation alone, or operation followed by radiation, was the method of choice. As a consequence, with two or three exceptions where a patient positively refused operative interference, all the patients have been treated by operation, whether radiation was given prior to, or subsequent to, the operation or not given at all. The patients who have been treated with radium alone have been those where a technical operative condition existed but the general condition of the patient made operation unusually hazardous. The chief disabilities in our group were old age and corpulence, high blood-pressure, organic heart disease, diabetes, and nephritis.

Eleven cases were treated by operation alone; forty-six cases by radium alone; eleven cases by radium and operation; and five cases by operation and radium.

Cases Treated by Operation Alone.—There were eleven of these cases, five less than five years old all are still living. Of the six remaining cases, three are living, one died from operation, one died from recurrence, and one has been lost sight of. "Known living after five years represents 50 per cent. of the total. Excluding the case lost sight of from consideration, the operative five-year cure rate is 60 per cent.

Cases Treated by Radium Alone.—There were forty-six of these cases. Of these forty-six cases, nineteen have been treated within five years and will be excluded from consideration. Of the remaining twenty-seven cases treated prior to five years ago, fifteen are living, seven are dead from the disease, and five from other causes. Of the living cases, five have just passed the five-year period, one, six years, one, seven years, one, eight years, four, nine years, two, ten years, and one, twelve years. Of the seven cases dying from recurrence, practically all had metastases; one lived one year, two lived two years, two, three years, one, four years, and one, seven years after the treatments. Of the patients who died from other causes than cancer, four died of apoplexy, and one of diabetes. One of the patients lived a year, two for three years, and one for four years.

After five years, of twenty-seven patients, fifteen are living and well, and twelve are dead, making a rate of 55 per cent. living and 45 per cent. dead. If we exclude from our list the patients known to have died of other causes than cancer, the cure rate is 69 per cent. If the cases dying of other causes than cancer and with no evidence of cancer are put in the cured list, the rate of cure would be 74 per cent.

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Cases Treated by Radium and Operation.—There were eleven of these cases. Of these eleven cases, two have been treated within five years and will be excluded from consideration. Of the remaining nine cases treated prior to five years ago, five are living and well, two died of recurrence, one from the operation, and one has been lost sight of. The percentage living is 55.5 per cent. and if the lost-sight-of case is excluded, the cure rate would be 62.5 per cent. In most of these patients, operation was performed a few days after radiation; but in two cases, a period of 60 days elapsed between the radiation and the hysterectomy; and, although curettage had demonstrated the disease prior to operation, the uterus after removal was found clear of cancer on most careful pathological study.

Cases Treated by Operation and Radium.—There were five of these cases. Of these five cases, one has been treated within five years and will be excluded from consideration. Of the remaining four, all are well. One, however, had a recurrence which, at a subsequent treatment, was cleared by the radium.

Advanced Inoperable Cases.—By inoperability is meant local extensions without demonstrable metastases which render complete removal impossible. The extensions may be either lateral or over the vaginal walls. A number of these patients were given only palliative treatment. At the present time, we would be very much inclined to treat everyone by a plan which aimed to cure. Omitting from consideration fifteen cases treated within the last five years, there remain thirty-one. Of these thirty-one cases, we have been unable to trace four. Sixteen died within two years; three lived for longer than two years; three lived for longer than three years; and one lived for five years. Four cases are living and well, so far as clinical examination discloses, after five years. The first of these patients, well for five years, had a complicating fibroid. The uterus was the size of a six months' pregnancy. There was fixation to the left pelvic wall. The histological grading was No. 1. The second case was inoperable as the entire uterus was involved and the condition extended down on to the vaginal wall. There was no fibroid present but the uterus was the size of a four months' pregnancy. Within three years, the uterus was of normal size and at the end of five years the patient still is well. The histological grading was No. 3. The third case has already been referred to and is well six years after treatment. Inoperability here was due to local metastatic glands on the pelvic wall found at the time of hysterectomy. The fourth case was inoperable because of fixation through the right broad ligament to the pelvic wall. This was grade No. 2 and the cure has lasted for five years. The five-year cure rate is 12.9 per cent. in this group. Taking the entire group of forty-six cases, and taking one year as the period of cure, the rate is 21 per cent.

Recurrent Cases.—Out of a total of thirty such patients, twenty-four have been treated more than five years ago. Twenty-two are dead; two are living and well. Of those that died, one lived three years, and one lived seven years; the others all died within two years of the time of the treatment. One of the cured cases has been well for six years and one for nine

years. The cure rate is 8.3 per cent. Our results in this group have been disappointing. When the patients came to us in most of the cases the disease seemed limited to the vagina and, practically without exception, the vaginal metastases cleared up. In some cases these were followed by local recurrences and in some by abdominal metastases. All died of the disease.

Cases Already Presenting Metastases.—There were eleven of these patients. In not one was a cure obtained. The metastases have been mainly to the pelvic glands and to the abdominal viscera and glands. In most of these patients, there was no attempt made to treat the whole disease but merely to relieve the chief complaint—usually pain. In a patient at present under observation, a large pelvic mass has disappeared and an upper abdominal metastasis has almost disappeared. In the very nature of things, however, the extensive metastatic cases are hopeless from the standpoint of cure. All of these patients of whom our records are complete died within two years of the time of the first treatment.

General Consideration.—Taking all cases, operable, inoperable, recurrent and metastatic which were treated prior to five years ago, there are included 112. Of these, ninety-one have died and twenty-one are living. We have not included in the living any cases except those known to be free of the disease. As already has been noted in the operable group, a number of patients died after some years of other causes than cancer. I have not included in these 112 cases those treated in any other way than by radium. The cure rate for the entire group is 18.7 per cent.

A study of our cases does not give us a great deal of encouragement in attempting either to prognose the outcome or to determine the radio-sensibility by grading of the cases. We have observed extensive metastases with grade No. 1's, we likewise have seen grade No. 4's which long have remained local. Our five-year cures represent all four grades.

As with cancer everywhere, the chief factor in determining the probability of cure treatment is the extent of the disease, the earlier the patient comes for treatment, the greater the likelihood of cure.

In operable cancers of the body of the uterus, radiation offers a method of treatment comparable to the best surgical treatment in its permanent results. It obviates, to a large measure, at least, primary mortality and is applicable to a large number of patients who are bad surgical risks.

Radiation offers a possibility of cure in a considerable percentage of inoperable and recurrent cancers of the body of the uterus.

In metastatic cancer, radiation can be a valuable palliative remedy, relieving pain, hæmorrhage, and probably prolonging life.

Pre-operative radiation does not increase the hazards of operation, and post-operative radiation would seem to be a logical procedure in many cases.

Where there is lateral trouble, evident on examination, and a doubt as to whether it is malignant or not, operation is preferable to radiation.

THE COMBINED RADIUM AND RÖNTGEN TREATMENT OF CANCER OF THE CERVIX UTERI

BY JAMES HEYMAN, M.D.

OF STOCKHOLM, SWEDEN

FROM THE RADIUMHEMMET OF STOCKHOLM.

IN THE early years of gynecological radiotherapy there were constant discussions as to the limits of the zone in which radium was therapeutically effective. It was frequently observed that carcinomata which were strictly limited to the cervix yielded better results than those where the cancer had spread to parametria and glands. This fact was in the first place considered to be due to an insufficient depth dose, the cancer cells at a certain distance from the radium not receiving a sufficient dose. True, the experience of recent years has taught us that an effective radiological treatment is by no means a problem of dosage alone, in the sense that it is only a matter of applying the greatest possible radiation intensity to all layers of the tumor, though it is natural to assume that in some cases an incomplete cure in intragenital radium treatment must be due to an insufficient depth dose. One is led to this assumption by the fact that not infrequently the cervical tumor itself disappears after treatment while the cancer continues to invade the parametrium and the glands. A more efficacious radiation of the parametria in these cases ought therefore to improve the results. The question of homogeneous irradiation of the pelvis is still a subject under discussion in gynecological radiotherapy.

Not long after Forssell, in 1913, had elaborated our present technic in the radium treatment of cancer of the cervix, we found that we were unable to attain the desired therapeutic effect in the parametria by increasing either the radium quantity or the duration of irradiation. These procedures only led to such an increase of the surface dose that injuries to the tissues in the neighborhood of the focus resulted especially to the bladder and rectum.

We learned that an aggregate vaginal and intra-uterine dose of about six 900 milligram element hours (115 milligram radium element for sixty hours) could not be exceeded without risk.

In order to obtain a more effective irradiation of the parametria it would have been necessary either to alter the technic in the intragenital application or to combine the intragenital application or to combine the intragenital treatment with irradiation of the parametria from some other entrance field.

The former of these alternatives, particularly the possibility of establishing a better relationship between surface and deep dosage through heavier filtration, we considered unwise to adopt, however, at that time. This was partly owing to the fact that we had only relatively small quantities of radium at our disposal, but the main reason was that we felt disinclined to depart

from a technic which held out such promising results before it had been tested on a larger number of cases.

The introduction of deep Röntgen therapy opened up new roads for parametric irradiation. In Germany, about fifteen years ago, the homogeneous irradiation of the pelvis by Röntgen-rays was the dominating question in gynæcological radiotherapy. This was partly owing to the difficulties this country encountered in procuring radium during and after the war. It is scarcely any exaggeration to say that the endeavor of the German gynæcologists to obtain a homogeneous Röntgen irradiation of the pelvis has been one of the most important incentives to the elaboration of modern deep Röntgen therapy (Seitz and Wintz, Krönig and Friedric, Warnekros and Dessauer).

As soon as Radiumhemmet, in the beginning of 1918, had obtained its first outfit for deep Röntgen therapy, the combined Röntgen and radium treatment of cervical cancer was tried in a large number of cases of cervical cancer. In the first instance these were chosen from among those where the previous radium treatment had failed (Rö. I).

During the period 1914-1925, 200 out of 885 cases were treated in this way and every new contribution to the Röntgen technic stimulated us to further efforts. The results, however, have been depressing. In only a few of these cases has a permanent cure been obtained whether there was a question of local or parametric recurrences or of metastases. Occasionally the Röntgen treatment may have inhibited the process or alleviated the pains for a short time, but the effect has been only temporary. A carcinoma which is not cured by our routine radium treatment is practically always refractory to Röntgen rays. This has also been our experience in recent years since we have been using a heavier filtration (filter equivalent to three millimeters of copper).

The above cases, however, are mentioned only in passing as they were not subjected to Röntgen treatment combined with the radium, but received Röntgen treatment only subsequently to radium, as a last resort. The aim of the present investigation is rather to find out whether Röntgen irradiation of the parametria given in direct connection with radium has been a valuable therapeutic adjunct or not. That question must be settled by comparing the end-results in two series of cases, one treated solely by radium, the other treated both by radium and Röntgen rays.

The difficulty in an investigation of this nature lies in the fact that one must have two relatively large series of cases for comparison, observed for at least five years. Furthermore the initial material must be equivalent and the radium technic the same in the two series. Investigations hitherto published on this subject do not seem to me to fulfil these conditions. Our experiences may therefore be of interest, the more so, as, on the one hand, the combined radium-Röntgen treatment is at the present time the form of treatment most in use, and, on the other, because our first impression of the combined therapy was not altogether favorable.

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I have mentioned before on different occasions (*Jour. of Obstet. and Gyn. of the Brit. Emp.*, vol. xxxi, No. 1; *Acta Radiologica*, vol. x, fasc. I, No. 53; and *Proc. of the Royal Soc. of Med.*, vol. xxii) that we tested the combined treatment for a few years but later restricted it to cases with large glandular metastases. The reason for this was mainly that in examining the primary results we were unable to find that the Röntgen treatment had brought about any improvement. A contributory cause was the occurrence now and then of cases of Röntgen cachexia undoubtedly due to a too forced Röntgen treatment. To what extent our reported views of the value of parametric Röntgen application must be corrected will be clear from the following account of the five-year results now available.

Our experiments with combined radium and Röntgen treatment were carried out mainly during 1919 and 1920. A smaller number of cases was treated during 1918, 1921, and in the beginning of 1922. During 1918-1920 our radium technic remained practically unchanged. In 1921 we began our therapeutic attempts at a modified radium treatment, of which an account was published in *Acta Obstet. et Gyn., Scand.*, vol. ix, fasc. 1-4. This modification consisted in giving two instead of three applications of radium. Only a few of the cases thus treated are included in the following statistics. As no other important change in our radium technic has occurred simultaneously with the Röntgen experiments, it may be assumed with fairly great probability that variations, if any, in the therapeutic results may be ascribed to the parametric Röntgen irradiation.

During the period 1918-1922 inclusive, 168 (36.8 per cent.) of a total number of 457 cases of cancer of the cervix admitted for treatment have been treated with combined radium and Röntgen irradiation. This will in what follows be called the combined treatment.

Table I shows the distribution of cases.

The cure result of the combined treatment on the five-year basis is forty-nine cured out of 168 treated. If we now compare this result with the five-year result for the cases numbering 289 treated from the start solely by radium during the same period (1918-1922 inclusive) we find: With radium alone, 21.8 per cent. five-year cures; with combined treatment, 29.2 per cent. five-year cures.

Before venturing upon any conclusions from this comparison, it will be necessary to show that the initial material in the two series is approximately equivalent.

During the period 1918-1922 inclusive, the cases were distributed as follows:

	Radium only	Combined treatment
Inoperable cases	62.6 per cent.	64.3 per cent.
Border-line cases	6.6 per cent.	8.3 per cent.
Operable cases	30.8 per cent.	27.3 per cent.

The series of cases subjected to combined treatment include a slightly larger number of advanced cases than that in which radium only has been

used. In spite of this, however, the end-result with the combined treatment is decidedly better. From this one might feel justified in concluding that the combined treatment is superior to radium alone.

Against this, however, it might be rightly argued that the number of cases in the two series is not sufficiently large. It is quite conceivable of course that chance coincidences of different kinds, *e.g.*, some intercurrent deaths or cases where it has been impossible for some reason or other to carry through the treatment rationally, may make the result in the series of cases treated solely with radium appear worse than in the series subjected to the combined treatment.

It has seemed to me appropriate, therefore, to find out what the outcome would be of a comparison between larger series of cases.

If the apparently better end-result of the combined treatment is really due to the parametric Röntgen irradiation, then the end-result during 1918-1920 inclusive, when the combined treatment was that mainly employed, ought to be better than the average result during the other years.

I have therefore compared the results from the period 1918-1920 inclusive during which time the combined treatment, as will be clear from Table I, was used in 66.2 per cent. of cases, with the result obtained in the total number of 737 cases treated during the ten-year period 1914-1923. It is true that during all these ten years the radium treatment has not been carried out in so strictly uniform a manner as during the period mentioned above and, further, that this series also includes the cases treated by Röntgen. However, the errors occasioned by these two factors are likely to outweigh one another. Also such chance coincidences as mentioned above may be considered eliminated in this relatively large series.

This comparison shows:

1914-1918 inclusive	23.1 per cent. five-year cures.
1914-1920 inclusive	26.8 per cent. five year cures.

During these two periods the cases were divided as follows:

	1914-1923	1918-1920
Inoperable cases	66.8 per cent.	66.7 per cent.
Border-line cases	7.7 per cent.	8.5 per cent.
Operable cases	25.5 per cent.	24.9 per cent.

It will be seen, therefore, that the initial material is almost identically the same.

This comparison, too, is in favor of the combined treatment. Our original opinion of the value of the parametric Röntgen irradiation, based on the primary results obtained, can no longer, therefore, be maintained. No other conclusion can apparently be drawn from my investigation than that the combined treatment has brought with it a more favorable end-result than intragenital treatment by radium alone.

It is to be noted, however, that the superiority of the combined treatment is by no means so obvious as has been suggested in some quarters.

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There is no doubt whatever that radium irradiation is by far the more important part of the treatment.

In my statistical examinations I have also tried to find an answer to two more questions:

Firstly, whether the parametric irradiation has improved the result in all the various stages of cervical carcinoma.

And secondly, whether any one particular variation in the Röntgen technic employed has yielded better results than any other.

With regard to the first of these questions it is of interest to find out whether the demonstrated superiority of the combined treatment is equally obvious in the operable as in the inoperable cases.

As in the group of operable cases no involvement of the parametria is clinically obvious, it might seem as if irradiation of the parametria would be unnecessary in these cases.

In the subjoined tables I have compared the result of the combined treatment, on the one hand, with the average result from the whole period, 1914-1923, when radium was the treatment mainly used and, on the other hand, with the result of radium treatment alone during the period 1918-1922.

In so doing I have included the operable and inoperable cases but left out the few border-line cases, for during the period 1918-1922 these numbered only thirty-three while the inoperable cases numbered 289 and operable 135.

The distribution of cases in the three series (border-line cases excluded) will be clear from the following table:

TABLE I

	All cases 1914-1923		Treated by radium only 1918-1922		Combined treatment 1918-1922	
	Number of cases	Cured	Number of cases	Cured	Number of cases	Cured
Inoperable...	492	64	181	17	108	19
Operable.....	188	82	89	37	46	24

I give this table only to show the number of cases within the different groups. As will be noticed, especially in the operable cases, the primary figures, on which the cure rate in the following table has been calculated, are small, thus reducing to some extent their proof value.

TABLE II

The Cure Result in Inoperable and Operable Cases with Combined Treatment Compared with the Average Result 1914-1923 and the Result of Radium Treatment Alone During 1918-1922

Cure rate	All cases 1914-1923	Radium only 1918-1922	Combined treatment 1918-1922
Inoperable.....	13.0	9.4	17.6
Operable.....	43.6	42.8	52.1

Table II shows that the combined treatment gives better results, both in inoperable and in operable cases. This fact is more marked in the inoperable series, although a not inconsiderable improvement is noted also among the operable cases. It would seem justifiable to conclude from the relatively large number of inoperable cases, and the considerable improvement of the results in this group, that the combined treatment of inoperable cases is superior to radium treatment alone. With regard to operable cases it seems doubtful whether any conclusion can be drawn. It is perhaps more prudent to wait until a larger series of cases which have been subjected to the combined treatment is available.

The technical procedure in applying the Röntgen treatment during these therapeutic attempts has varied in several respects. These variations refer in the main to the number of entrance fields, the number of irradiations and their distribution in series, the interval between the series, and lastly, the time of application of the Röntgen in relation to the radium treatment. I am going to deal only with the last of these factors. With regard to the other factors, it is not possible to divide the available material into groups large enough to allow conclusions to be drawn.

In one series, the larger one, the Röntgen treatment has been given during the three weeks that, according to our standard technic, are allowed to elapse between the second and the third radium application. This form of treatment has been designated Rö. III in our tables. In a smaller series of cases the Röntgen treatment was started after the third radium application, not later than one month after, usually within fourteen days (Rö. II).

TABLE III

Combined Treatment. Röntgen Treatment After the Third Radium Application (Rö. II)

	Number of cases	Cured (5 years)	Cure rate
All cases.....	53	17	32.1 per cent
Of which: inoperable.....	39	9	23.1 per cent
border-line.....	4	2	50.0 per cent
operable.....	10	6	60.0 per cent

We have also tried to start with Röntgen treatment and to give the radium subsequently (Rö IV). On account of various circumstances these cases have been relatively few in number and will not be included in what follows.

In Table III and Table IV the figures referring to the two series above mentioned are submitted.

TABLE IV

Combined Treatment. Röntgen Treatment Between the Second and Third Radium Application (Rö. III)

	Number of cases	Cured (5 years)	Cure rate
All cases.....	115	32	27.9 per cent
Of which: inoperable.....	69	10	14.5 per cent
border-line.....	10	4	40.0 per cent
operable.....	36	18	50.0 per cent

TREATMENT OF CANCER OF CERVIX UTERI

The results in the two series have been compared in Table V.

TABLE V
Comparison Between the Cure Results in R_ö. II and R_ö. III

	R _ö . II	R _ö . III
All cases.....	32.1 per cent	27.9 per cent
Inoperable.....	23.1 per cent	14.5 per cent
Border-line.....	50.0 per cent	40.0 per cent
Operable.....	60.0 per cent	50.0 per cent

It will be clear from the comparison made in Table V that the end-result throughout is somewhat better in the first group (R_ö. II) than in the latter.

True that the border-line and operable cases are few in number, and the relatively slight difference as regards the cure result may conceivably be due to some chance coincidence. On the other hand, the difference in the cure rate in the comparatively large group of inoperable cases is sufficiently well marked to show that the form of combined radium-Röntgen treatment where the Röntgen is given after the completed radium treatment is to be preferred.

Our experiences have led us to combine, since 1929, our radium treatment with Röntgen irradiation of the parametria as a routine, at least in inoperable cases, and to start the Röntgen treatment within a month of the final radium application.

These attempts with combined radium-Röntgen treatment were commenced simultaneously with the introduction of the deep Röntgen therapy at Radiumhemmet. Our therapeutic technic has developed with the rapid improvement in technical resources during these years and has gradually become modified according to experience gained. It is beyond the scope of this investigation to relate in detail how this technic has varied. The majority of cases has been treated on fairly uniform lines as far as the more important factors in the technic are concerned.

The following conditions prevailed in most cases during the period 1918-1922: Inductor coil with gas tube (S.H.S.). Peak voltage, 160-180. Milliamperage 2-2.5 milliamperes. Filter: during 1918, 4 millimetres aluminium, from 1919 inclusive 0.5 millimetre copper + 1 millimetre aluminium. Skin-focus distance: at first 20 centimetres later generally 30 centimetres.

In all cases two abdominal fields were used, in nearly all of them in addition two posterior fields and occasionally also a perineal field were used. The fields have nearly always been rectangular, varying between 10 and 13 square centimetres. The depth dose at 10 centimetres depth and at a skin-focus distance of 20-30 centimetres is estimated as 20-25 per cent. of the skin dose.

Dosage.—During the years under review the dose was measured at Radiumhemmet by Holzkecht's units and tablets. According to statistical data pertaining to the Röntgen dosage in Sweden (Sievert: *Acta Radiologica*, vol. vii, p. 401) one S.U.D. approximately corresponds to fifteen to sixteen Holzkecht units. With the radiation intensity attained at that time it may

be assumed that one S.U.D. with 4 millimetres aluminum corresponded to about 600 Behnken's units and with 0.5 millimetre copper + 1 millimetre aluminum to about 700 Behnken's units.

The skin dose at each application was: ten Holzkecht units, occasionally fifteen Holzkecht units, exceptionally five Holzkecht units.

The number of fields in each series of treatments was usually four, two anterior and two posterior. Only one application was given daily. A series consisted of one application to each field, in all four applications the fields being irradiated in rotation. Usually two series were given consecutively, each field thus generally receiving a total of twenty Holzkecht units. Some of the earlier cases received three series consecutively. Subsequent experience regarding the local as well as general reaction of the patients caused us, however, to interpose an interval of one or several months between the second and third series.

In cases proceeding favorably it gradually became the rule not to repeat the treatment after the conclusion of two series. With the more powerful apparatus that came into use later and the consequently much increased radiation intensity, we deemed it appropriate to reduce not only the single dose but also the aggregate dose per field and further to reduce the number of irradiated fields.

Since 1929 the following technic has been in use:

Transformer with valve-tubes and condensers. Coolidge tube. Constant voltage 160-170. Milliamperage: 6 milliamperes. Filter: Thoracuss' tin-filter equivalent to three millimetres copper (*Abstracts of Communications, Second Radiological Congress, 1928*). Skin-focus distance: 30-40 centimetres according to the thickness of the abdominal wall. No compression.

Entrance fields: Two abdominal, 10 to 13 square centimetres. Beam centered on the subjacent parametrium.

Each field receives 3 by $\frac{1}{4}$ S.U.D. Only one field is irradiated per day, left and right alternately. If the patient's general condition is appreciably affected the treatment is stopped for a day or two; as a rule, however, the Röntgen treatment can be carried out in the course of six consecutive days. In advanced cases or in cases where the radium treatment does not seem to be yielding the expected result, it may be necessary to give a larger Röntgen dose. This can be done by irradiating two posterior fields provided the patient's general condition and blood picture remain good. All patients are kept under careful observation and as long as they are progressing favorably the treatment is not repeated.

For the time being this method of irradiating the parametria will form a routine part of our treatment for inoperable carcinoma of the cervix. Until we have gained sufficient experience most operable cases will be similarly treated.

To what extent treatment by Röntgen may be replaced in the future by treatment by radium at a distance will depend upon the outcome of experiments which we have recently started.

TREATMENT OF CARCINOMA OF THE CERVIX UTERI

BY WILLIAM P. HEALY, M.D.

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HAS the question of treatment for carcinoma of the cervix uteri been settled? If not, what are the chief differences of opinion and the reasons therefor?

Briefly, it may be said that, previous to the discovery of radium and the subsequent recognition of its therapeutic qualities in the treatment of cancer, the only methods of treatment in vogue for cancer of the uterine cervix were those dependent upon surgical procedures. There were cautery operations, such as the high amputation of the diseased cervix with the actual cautery, as advocated and practiced by Byrne, or the slow, complete destruction of the growth by the prolonged application of heat with a hot soldering-iron, according to the method of Percy. There was the operative removal of the entire uterus with its adnexæ and the adjoining parametrial connective tissues and lymphatics by vaginal route (Schauta) or by the abdominal route (Wertheim).

There was also a combination of cautery and surgical treatment in which the cervical lesion was first thoroughly destroyed by heat and then the hysterectomy was done either at once or shortly after.

The success attending any one of the procedures mentioned varied with different operators, but, on the whole, the problem was most discouraging as the cures were so few and the failures so many.

The chief obstacle to success was the same then as it is today—the disease had become too extensive before it was recognized.

The absence of symptoms which would enable the physician to recognize the disease while it was still localized at its original site and before it had spread to adjoining structures and neighboring lymph-glands accounted for the high percentage of advanced and therefore incurable cases.

Nevertheless, specialists in pelvic surgery attacked this discouraging situation with courage and resourcefulness and finally the splendid operative procedure known as the Wertheim abdominal hysterectomy was developed and perfected in 1898.

Fundamentally, this consists not only in the removal of the uterus and adnexæ, but also the clearing out of all the parametrial connective tissues, lymphatics and regional lymph-glands and the amputation with the uterus of the upper third of the vaginal tube. This operation required the recognition and exposure of both ureters throughout the greater portion of their pelvic course and it interfered greatly with the support and innervation of the bladder. It was an extremely tedious and, indeed, difficult surgical procedure. The result was a high primary operative mortality which was entirely out of proportion to the benefit to be expected for those that survived. This

was not to be wondered at when it was realized that 40 to 60 per cent. of the cases in which operation was attempted had already developed regional lymph-gland metastases.

A study of gynecologic literature from 1900 to 1920 will show that earnest and conscientious efforts were made by competent surgeons to cure carcinoma of the cervix by means of the Wertheim hysterectomy and that the end-results were far from satisfactory to the surgeon.

There is no doubt, however, that this procedure increased the operability rate so that many more cases were subjected to major surgery under this plan than previously. In fact, Bonney thinks the operability rate increased to 50 per cent. or more. Bonney is probably the outstanding exponent today of the Wertheim plan of treatment for carcinoma of the cervix. He is a surgeon of unusual skill and judgment, he has earnestly and conscientiously applied himself to the development of a technic which would permit him to obtain the best possible results by surgical methods, and he has been able to reduce the primary mortality in his last five-year series to 16.5 per cent.

BONNEY did his first Wertheim in 1907. In the twenty-three years from 1907 to 1929, inclusive, he did the operation 382 times. He thinks his operability rate is 63 per cent. or more, so that during those twenty-three years he saw about 450 cases. This would leave a very large number of cases of carcinoma of the cervix in England available for operation during those years by other surgeons, but very few reports are available.

Bonney gives two reasons in explanation for the extremely small number of papers from surgeons dealing with a large series of Wertheim operations. Both reasons seem inadequate and fail to explain. It would seem more probable that surgeons have no large series of Wertheim operations to report, as they have, after giving it a fair trial, been discouraged and therefore discarded the operation as a routine treatment for carcinoma of the cervix for good and sufficient surgical reasons. These reasons have been stated many times in the past twenty-five years and are also emphasized in Bonney's Hunterian Lecture. They are, briefly, the distressing post-operative sequelæ in the form of sepsis, ureteral, vesical and intestinal fistulæ, long period of invalidism, and high primary mortality.

These unfortunate and serious complications may be expected with confidence since they occur in the practice of all surgeons who attempt the operation, even the most expert, including Bonney himself. Under those circumstances, surgeons and gynecologists of recognized skill and experience who have, with patience and great courage, attempted to cure carcinoma of the cervix with the Wertheim operation, have given it up as an unjustifiable routine surgical procedure.

Bonney's five-year statistics—284 operations to the end of 1924—show a primary mortality of 16.5 per cent. and a cure rate of 28.7 per cent.

With the discovery of radium and the advent of radiation therapy in the treatment of cancer, it was a natural sequence that methods were devised looking toward control and cure of carcinoma of the uterine cervix by radiation therapy.

In Europe, Regaud, Forssell, Heyman, Döderlein, and in the United States, Kelly, Burnam, Schmitz, John Clark, Bailey—all were pioneers in developing various plans of attack upon the disease and different methods of radiation therapy.

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The anatomical location of the cervix, its accessibility and the presence of the cervical canal, permitting attack from within as well as without and the fact that the cervix had no vital function to perform—all tended to create a situation favorable for study and treatment of the disease.

Finally, from the various clinics under control of the investigators named, as well as from other clinics, reports favorable to radiation therapy began to appear. As was to be expected, at first these reports dealt only with the treatment of advanced or inoperable cases, as the favorable cases still were subjected to operation.

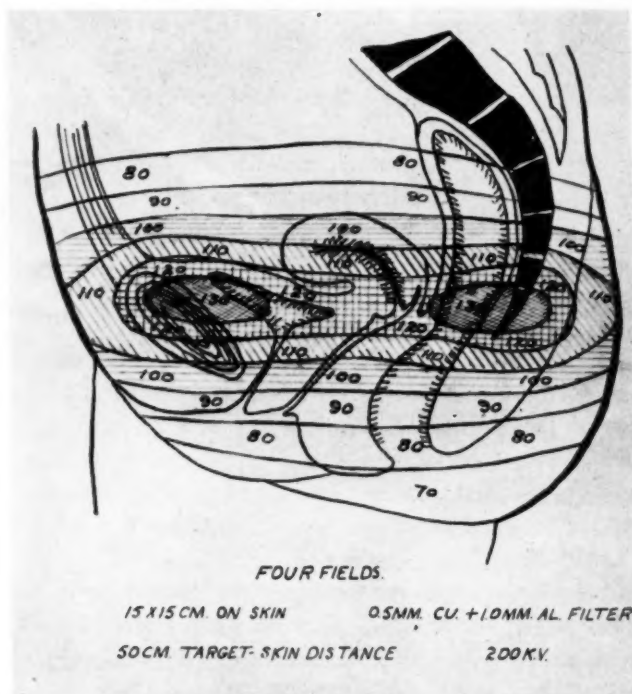


FIG. 1.—Sagittal section of average female pelvis. Showing distribution of radiation from X-ray pelvic cycle—four fields—15 by 15 centimetres on skin, 200 kilovolts, 0.5 millimetres copper and 1 millimetre aluminum filter, 50 centimetres target-skin distance. One erythema dose to each area.

The palliative results were so surprisingly satisfactory that inevitably less and less advanced cases were accepted for such treatment. Finally, because of the good results obtained with them and the absence of primary mortality and serious complications, even the early and most favorable cases were subjected in many clinics to radiation therapy instead of operation.

Radiation therapy has been, no doubt, somewhat handicapped because of the great cost of radium. Nevertheless, enough of the element has been available in different institutions in Europe and America since 1915 to permit large series of cases of carcinoma of the cervix to be treated with radium alone or in combination with Röntgen-ray. Papers dealing with the ex-

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perience of the surgeons in these institutions have been published from time to time and we now have available for study a rather voluminous literature from all over the world covering the treatment of cases with radiation therapy only, the number of which now reaches into the thousands.

Incidentally, the establishment of radiation therapy has also placed upon a firm basis the importance and necessity of an accurate follow-up clinic, and has emphasized the value of a well-organized social service department for keeping in touch with the patients, especially of the poorer financial class.

As experience in the radiation therapy of carcinoma of the cervix has accumulated, it has been realized that a large amount of radium is not essential in the treatment of an individual case, but that 150 milligrams of the element disposed in needles and capsules of different strengths, thus permitting them to be used in applicators of various shapes and sizes, are quite sufficient for thorough treatment of any case of carcinoma of the cervix, especially if it can be combined with deep Röntgen-ray therapy by means of the high-voltage machine.

This is important from the economic standpoint, as it permits the treatment to be carried out by physicians or medical groups in many centres of population instead of restricting it to large institutions.

Nevertheless, it may here be quite properly pointed out that the large institution or hospital devoted exclusively to the study and treatment of cancer and allied diseases has a most important function to perform from the standpoint of research and education as well as treatment.

Such institutions, with their large laboratories and staffs of trained specialists, not only elucidate obscure problems and develop new methods of technic, but offer to the medical profession facilities for advanced study as internes and as post-graduate students.

From Radiumhemmet, in Stockholm, there have been a number of interesting and valuable reports by Forssell and Heyman concerning their experience with radiation therapy in carcinoma of the cervix.

HEYMAN, in a study of 3,184 cases of cancer of the cervix uteri, radiologically treated, collected from thirteen clinics, concluded that permanent healing for a period of five years or more may now be counted on with the technic generally employed in about 16 or 17 per cent. of the total number of applicants.

The absolute healing percentage obtained at Radiumhemmet in 500 cases was 22.4 per cent. for five years or more.

Heyman emphasizes the important difference in the character of the material dealt with in computing end-results in cases treated surgically or by radiation therapy.

The surgical statistics nearly always deal with series of cases of high operability, usually 50 to 60 per cent. of the cases being regarded as operable, whereas the operability percentages in cases treated by radiation therapy are, in the majority of instances, less than 30 per cent.

Heyman concludes from a study of surgical and radiation percentages as to end-results in different clinics throughout the world that primary healing obtained by radiation therapy is just as permanent as is surgical healing. This is important.

Results at Radiumhemmet depend almost exclusively upon the use of radium alone

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without X-ray or operation. As to the treatments, two or three in number are given in the course of a short time, at most from three to four weeks.

The last report from Radiumhemmet gives the following five-year end-results: Absolute cure rate in the treatment of carcinoma of the cervix, 20.6 per cent.; cure rate in operable cases of carcinoma of the cervix, radiologically treated, 40.4 per cent.

It is now fully established that the most important factor controlling the permanence of cure, regardless of the method of treatment employed, is the clinical or gross extent of the disease when treatment is begun. Thus, early diagnosis establishes ground for a good prognosis in 60 per cent. of the cases.

In addition, however, a study of end-results obtained in cases treated by radium alone or in combination with X-ray has led to the conclusion by some investigators (Healy and Cutler) that the histological structure of the

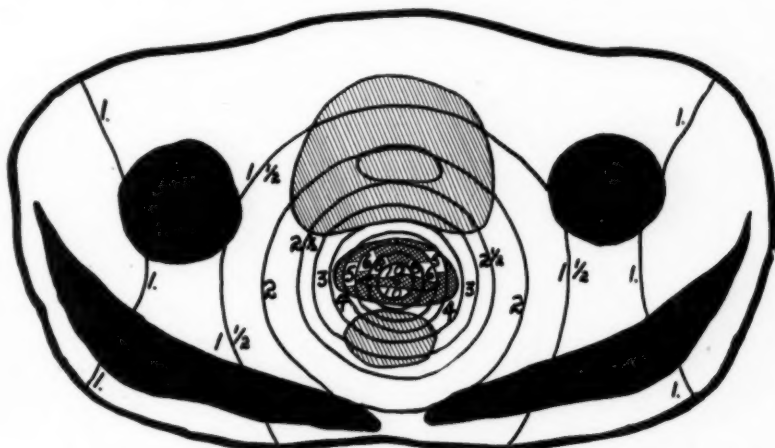


FIG. 2.—Tissue doses delivered throughout the average female pelvis by radiation given as follows: (1) Vaginal bomb=3 positions, 1000 millicurie-hours in each; (2) intra-uterine tandem=1000 millicurie-hours from upper tube, 2000 millicurie-hours from lower; (3) X-rays.—High voltage pelvic cycle, four fields, 1 skin erythema dose on each. Stated in terms of skin-erythema dose. (One-fourth life-size.)

tumor has a decided bearing upon prognosis, especially in advanced cases, when radiation therapy is the method of treatment employed.

For a long time, it was felt that the difference noticed in the response of cases of cancer of the cervix to radiation therapy could be explained in various ways but finally it was recognized that many of the tumors must be regarded as being especially radiosensitive judging by their rapid and often-times complete disappearance after treatment.

About 96 per cent. of all cases of cervical cancer belong histologically in the squamous epidermoid cancer-cell group. The remainder are classified as adenocarcinoma.

The tumors which seem to be most radiosensitive are those in which the histological structure is of the embryonal or immature cell type with marked evidences of anaplasia and little stroma. These, it is also interesting to note, are regarded histologically as the most malignant.

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Possibly 17 to 20 per cent. of all cases of cervical cancer are in the very radiosensitive group.

The sensitivity to radiation seems to diminish as the cell type becomes more mature and more like the fully developed adult squamous cell.

This is the most resistant cell type to radiation therapy in the cervix and includes about 20 per cent. of all cases. The remaining 60 per cent. of cases between the two groups referred to may vary in response to radiation therapy

according to the proportion of the two types of cells, embryonal or adult, present, or of cells resembling or approaching one or the other group in histological characteristics.

That these two factors, early diagnosis and histological structure of the tumor, are not the only important factors influencing end-results is indicated by the large number of apparently favorable cases that die (25 to 40 per cent.) within five years after treatment, even when this has been promptly instituted.

It would appear from the high percentage of fatalities resulting from recurrence of cancer in the early or operable group within five years of the treatment, whether radiological or surgical,

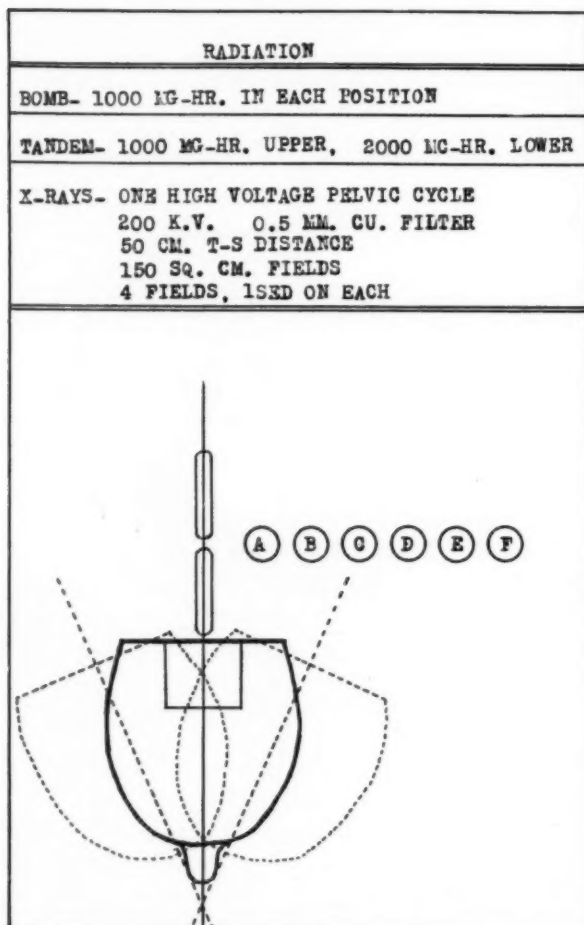


FIG. 3

that we cannot be satisfied with our present method of treatment.

These fatalities seem to be due to metastases which have occurred early in the course of the disease but which have eluded the surgeon's knife or have resisted the action of radium and X-ray, despite the fact that such metastases must be extremely small in order not to be recognized.

In the majority of instances, the recurrences are in the lymphatic glands of the broad ligaments or in the presacral and prevertebral lymphatic glands.

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At times the recurrence is situated in the cellular tissues surrounding the outer end of the vaginal canal, just within the hymen.

Recurrences located about the vaginal vault or along the vaginal canal after hysterectomy are often amenable to radiation therapy. In Bailey's series, 1918 to 1921, 139 cases were treated with radium alone for post-operative recurrences and sixteen cases, or 11.5 per cent., remained well for six to nine years.

On the other hand, in our experience, retreatments for local recurrences after full radiation therapy for the primary lesion do not seem to be satisfactory. This is also the opinion of Heyman.

In 1924, there were 150 cases of primary carcinoma of the cervix treated at the Memorial Hospital.

TABLE I

Cases of Carcinoma of Cervix, 1924

		Alive 1930	Per cent. Alive
Early	19	11	58
Border-line	23	6	26
Advanced	91	13	14.3
Palliative	17	0	—
Totals	150	30	

TABLE II

Absolute Cure Rate in Cases of Carcinoma of Cervix Treated in 1924

Cases Treated	150
Cases Cured	30
Absolute Cure Rate	20 per cent.
Absolute Cure Rate (Radiumhemmet)	20.6 per cent.

TABLE III

The Cure Rate in the Operable Cases of Carcinoma of the Cervix Treated in 1924

Cases Treated	42
Cases Cured	17
Percentage Cured	40.5
Percentage Cured (Radiumhemmet)	40.4

It will be seen from Tables II and III that the end-results obtained at the Memorial Hospital and the Radiumhemmet with regard to cures are alike.

As the attitude in each of these institutions is to treat all cases that apply, even if only for temporary palliation—and, in fact, very few cases are denied treatment—it is reasonable to assume that these statistics represent the best that may be obtained with our present methods of radiation therapy.

They will vary slightly from year to year, but, on the whole, they may be expected to remain stationary.

It would seem, then, that the outlook for cure of carcinoma of the cervix cases is not a happy one as a study of the leading surgical and radiation

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statistics indicates that by either method of treatment 80 per cent. of all cases seen will fail to survive five years.

It is recognized that an individual surgeon or radiation therapist may, by special ability or technic, obtain somewhat better end-results than the average. This does not, however, alter the seriousness of the problem, which, after all, must be met by physicians of average ability and resources.

TISSUE DOSES AT INDICATED POINTS							
POINT	APPLICATOR	% SED	% TOTAL	POINT	APPLICATOR	% SED	% TOTAL
A	BOMB - LEFT	15	2	D	BOMB - LEFT	5	2
	" CENTER	70	7		" CENTER	15	5
	" RIGHT	50	5		" RIGHT	40	15
	TANDEM-UPPER	235	25		TANDEM-UPPER	40	15
	" LOWER	470	50		" LOWER	80	29
	X-RAYS	100	10		X-RAYS	100	35
	<u>TOTAL</u>	<u>940</u>	<u>100</u>		<u>TOTAL</u>	<u>280</u>	<u>100</u>
B	BOMB - LEFT	10	2	E	BOMB - LEFT	5	2
	" CENTER	40	7		" CENTER	10	4
	" RIGHT	60	10		" RIGHT	30	13
	TANDEM-UPPER	120	21		TANDEM-UPPER	30	13
	" LOWER	240	42		" LOWER	60	26
	X-RAYS	100	18		X-RAYS	100	42
	<u>TOTAL</u>	<u>570</u>	<u>100</u>		<u>TOTAL</u>	<u>235</u>	<u>100</u>
C	BOMB - LEFT	10	2	F	BOMB - LEFT	5	2
	" CENTER	25	6		" CENTER	5	2
	" RIGHT	55	14		" RIGHT	20	10
	TANDEM-UPPER	70	17		TANDEM-UPPER	25	12
	" LOWER	140	35		" LOWER	50	25
	X-RAYS	100	25		X-RAYS	100	49
	<u>TOTAL</u>	<u>400</u>	<u>100</u>		<u>TOTAL</u>	<u>205</u>	<u>100</u>

TABLE IV

The fact remains that only twenty cases out of every 100 are salvaged for five years.

On the whole, the most important fact is the necessity for early diagnosis, as 60 per cent. or more of the early cases may be expected to survive five years.

In the final analysis, then, it would seem that the skillful surgeon, qualified by special training and experience, may obtain in the operable cases as many cures as the skilled radiation therapist, but the surgeon will always

TREATMENT OF CANCER OF CERVIX UTERI

have to combat a primary mortality much higher than that of radiation therapy, and also a much greater morbidity.

Two-thirds of the cases are not amenable to surgery and are treated best by radiation.

There are always twice as many cases, therefore, for radiation than for operation and as a result radiation therapists gain twice as much experience.

It is safe to say that today, despite the short time elapsed since the development of radiation therapy, there are more specialists qualified to treat carcinoma of the cervix properly with radium and X-ray than there are surgeons qualified to do a radical Wertheim hysterectomy.

This is in no wise a criticism of surgeons but is a natural outgrowth from a discouraging situation.

Radiation technic in the treatment of carcinoma of the cervix has made rapid strides and is no longer a hit-or-miss affair. The dosage to be obtained in different parts of the lesion and the pelvis can be determined with reasonable accuracy and the minimum amount of radiation necessary to take care of the lesion, measured in skin erythema doses, is fairly well known.

Fig. 1 indicates, in diagrammatic form, the distribution of radiation in an average female pelvis, from high voltage X-ray measured in skin erythema doses.

Fig. 2 indicates the total tissue doses delivered throughout the average female pelvis by combined radiation with radium applied directly to the lesion by means of vaginal and intra-uterine applicators and X-ray through four fields about the pelvis. The tissue doses are stated in terms of skin erythema dose.

Fig. 3 shows vaginal bomb applicator and intra-uterine radium tandem in position (actual size, diagrammatic).

See Table IV for doses delivered at lettered points two centimetres above external os and one to six centimetres distant from cervical canal.

In conclusion, it may be said that radiation therapy has a wider field of usefulness in the treatment of carcinoma of the cervix than has hysterectomy, as it may be used to advantage in the treatment of all cases, favorable and unfavorable for a cure.

The end-results in the favorable cases are, on the whole, somewhat better with radiation.

There is little, if any, place for hysterectomy in the treatment of advanced cases.

LES MÉTASTASES DES ÉPITHELIOMAS DU COL UTERIN LOCALEMENT GUÉRIS PAR RADIOTHÉRAPIE

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L'ÉPITHÉLIOMA du col utérin, abandonné à son évolution naturelle, aboutit à une terminaison fatale en peu d'années (2 à 3 en moyenne). La cause de la mort consiste ordinairement en une complication qui peut être: a) locale (hémorrhagie, infection) b) de voisinage (compression des urètres, envahissement de la vessie, du péritoine, de l'intestin); c) distante (métastases). Ce cancer suit donc les étapes classiques dans l'envahissement de l'organisme.

Les voies de la généralisation des épithéliomas du col ont été depuis longtemps et minutieusement étudiées. Il a été établi que la dissémination résultait rarement de l'irruption du néoplasme dans une veine. En revanche, l'envahissement des vaisseaux lymphatiques se produit précocement; les métastases sont l'aboutissant du cheminement progressif du cancer dans les voies lymphatiques: étape par étape, c'est-à-dire à travers les différents groupes ganglionnaires, les cellules cancéreuses atteignent la grande circulation par le canal thoracique. Habituellement, ce long circuit et les barrières ganglionnaires multiples retardent la généralisation; en outre, le siège profond de ces voies lymphatiques, la difficulté de leur exploration dissimulent pendant longtemps leur envahissement. Aussi la plupart des malades non traitées succombent-elles du fait des complications locales avant que la généralisation ait eu le temps de se manifester cliniquement. Mais l'autopsie révèle la fréquence des métastases latentes.

Dans la période que l'on peut appeler l'*ère chirurgicale* du cancer du col (qu'on peut faire débiter vers 1890 environ), de nombreuses et minutieuses recherches ont fait connaître en détails tous les embranchements du réseau lymphatique que sont susceptibles d'emprunter les cellules cancéreuses. La précocité de leur envahissement a été établie; il a été démontré, que dans une proportion importante des cancers considérés comme au début en raison de la limitation apparente des lésions, les ganglions régionaux étaient déjà pénétrés par des éléments néoplasiques.

L'*ère radiothérapique* de l'épithélioma du col, bien qu'encore récente, a déjà eu pour conséquence d'entraîner certaines modifications importantes dans la marche habituelle de ce cancer. C'est ainsi qu'à L'Institut du Radium de Paris, par exemple, trois étapes dans la technique radiothérapique des épithéliomas du col se sont succédées au cours de ces 10 dernières années; à chacune d'elles ont correspondu certains tableaux cliniques particuliers.

a) Les premiers résultats obtenus par l'emploi des radiations le furent au moyen de la curiethérapie: un foyer placé dans le fond du vagin ou dans

l'ulcération du col, amenait (dans un certain nombre de cas) la fonte des bourgeons néoplasiques et la cicatrisation des ulcérations. Mais, en ce qui concerne surtout les cancers étendus, ce blanchiment des lésions apparentes ne durait généralement que peu de semaines; après quoi se produisait une récurrence locale. En définitive, la thérapeutique avait temporairement enrayeré la marche de la maladie sans en modifier sensiblement le mode d'évolution.

b) Puis, dans une deuxième étape, la technique de la curiethérapie intracavitaire fut considérablement améliorée. Ces perfectionnements consistaient en l'emploi de foyers de radium faibles mais aussi nombreux que possible et fortement filtrés, en leur disposition rationnelle dans toute la longueur du canal au niveau de l'utérus et dans des positions d'élection fixes au niveau du vagin, en l'allongement sur plusieurs jours de l'irradiation continue. Conséquemment à ces progrès techniques, la guérison des épithéliomas au stade I devint presque régulière. Dans la plupart de ceux au stade 2, et même dans certains cas inopérables, on obtint la disparition des lésions perceptibles à l'exploration. Mais l'observation prolongée de ces malades mit souvent en évidence une évolution clinique particulière. Après six, huit mois, un an, ou même après plusieurs années, ces patients, dont l'état général était redevenu excellent, accusaient des douleurs sciatiques dont l'accentuation progressive tendait à les rendre intolérables; d'autres fois, une constipation opiniâtre représentait le premier signe anormal. L'exploration vaginale confirmait la disparition totale des lésions cervicales, mais le toucher rectal mettait en évidence la présence d'une tumeur profonde, tantôt présacrée, tantôt plaquée contre la paroi latérale de la cavité pelvienne et correspondant à une masse ganglionnaire hypogastrique.

c) A partir de 1924, et plus généralement en 1925, le traitement des épithéliomas du col inopérables consista dans la combinaison de la curiethérapie intracavitaire avec une irradiation pelvienne transcutanée, soit par röntgenthérapie, soit par curiethérapie à distance. Le résultat fut une augmentation importante de la proportion des guérisons de malades inopérables. Mais en même temps, un autre mode clinique d'évolution de l'épithélioma du col utérin augmentait de fréquence: la généralisation métastatique. C'est cette forme clinique que je me propose de présenter ici avant d'en discuter le mécanisme.

RÉSUMÉ DES OBSERVATIONS

Obs. 1° XIV A 34.—59 ans. Stade 2. *Épithélioma pavimenteux épidermoïde*. Traitement le 6 mai et le 9 octobre 1919 par curiethérapie intracavitaire (Ra interne). Guérison apparente pendant 3 ans. En 1922, douleurs abdominales; on constate la présence d'une petite tumeur lombaire prévertébrale: lent développement de cette masse au cours des années suivantes. En février 1925, il existe plusieurs autres tumeurs abdominales (épigastrique, iliaque). Persistance de la guérison locale. Mort en juillet 1926.

Obs. 2° XIV A 198.—42 ans. Stade I. *Épithélioma embryonnaire avec ébauche d'évolution épidermoïde*. Traitement le 10 décembre 1920. (Ra interne). En avril 1922, douleurs dans la région hépatique; en juillet, développement d'une tumeur du foie. Persistance de la guérison locale. Mort le 20 décembre 1922.

OBS. 3° XIV A 241.—42 ans. Stade 1. *Épithélioma pavimenteux épidermoïde*. Traitement le 5 novembre 1921 (Ra interne). En février 1923, douleurs lombaires: pas de signes à l'exploration du vagin et du rectum. A la fin de mars surviennent des phénomènes cérébraux: torpeur progressive, coma et mort par métastase crânienne probable le 9 avril 1923.

OBS. 4° XIV A 270.—55 ans. Stade 3. *Épithélioma pavimenteux épidermoïde*. Traitement le 27 mai 1922 par röntgénéthérapie et curiethérapie intracavitaire combinées (RX ÷ Ra interne). Guérison apparente pendant 3 ans. En juin 1925, apparition d'un ganglion sus-claviculaire gauche; présence d'une tumeur lombaire prévertébrale. A partir de juin 1926, signes de compression intestinale; apparition d'un ganglion axillaire gauche; crises d'épilepsie jacksonienne. Persistance de la guérison locale. Mort le 24 novembre 1926.

OBS. 5° XIV A 411.—59 ans. Stade 3. *Épithélioma pavimenteux épidermoïde*. Traitement le 28 janvier 1924 (RX ÷ Ra interne). Guérison apparente pendant 4 ans. En mai 1928, douleurs lombaires. A la fin de cette année, signes de métastases pulmonaires; persistance de la guérison locale. Mort le 10 janvier 1929.

OBS. 6° XIV A 432.—53 ans. Stade 4. *Épithélioma pavimenteux épidermoïde*. Traitement le 29 mars 1924 (RX ÷ Ra interne). Guérison apparente pendant 4 ans. En septembre 1928, douleurs abdominales. En octobre, se développe une tumeur épigastrique prévertébrale. Persistance de la guérison locale. Mort au début de l'année 1929.

OBS. 7° XIV A 525.—47 ans. Stade 2. *Épithélioma pavimenteux épidermoïde*. Traitement le 13 juin 1925 (RX ÷ Ra interne). En décembre 1925, douleurs abdominales: présence d'une tumeur de la fosse iliaque gauche. En février 1926, développement d'une tumeur lombaire prévertébrale. Persistance de la guérison locale. Mort le 24 avril 1926.

OBS. 8° XIV A 527.—46 ans. Stade 1. *Épithélioma non épidermoïde*. Traitement le 15 juin 1925: curiethérapie intracavitaire suivie d'hystérectomie. En juin 1926, douleurs lombaires: l'exploration du vagin et du rectum est négative. En février 1927, apparition d'un ganglion sus-claviculaire gauche; en octobre 1927, adénopathie cervicale droite: la palpation révèle la présence d'une masse lombaire prévertébrale. Mort le 19 octobre 1927.

OBS. 9° XIV A 531.—48 ans. Stade 3. *Épithélioma pavimenteux épidermoïde*. Traitement le 26 juin 1925 (RX ÷ Ra interne). En octobre 1925, apparition d'un ganglion sus-claviculaire gauche. Signes de métastases pulmonaires; persistance de la guérison locale. Mort le 4 avril 1926.

OBS. 10° XIV A 539.—57 ans. Stade 2. *Épithélioma de transition*.* Traitement le 7 août 1925 par curiethérapie intracavitaire et curiethérapie transcutanée combinées (Ra interne ÷ Ra externe). Guérison apparente pendant 3 ans. En décembre 1928, signes de métastases pulmonaires; persistance de la guérison locale. Mort en avril 1929.

OBS. 11° XIV A 556.—53 ans. Stade 3. *Épithélioma de transition*. Traitement le 20 octobre 1925 (Ra interne ÷ RX). Guérison apparente pendant 5 mois. En mars 1926, on perçoit par palpation abdominale, une tumeur lombaire prévertébrale. En juin 1927, la tumeur abdominale s'est développée et donne des signes de compression intestinale. Développement d'une tumeur épigastrique. Persistance de la guérison locale. Mort le 21 juin 1927.

* J'entends par épithélioma de transition une variété d'épithélioma qui prend ordinairement son origine dans la région endocervicale, au niveau du passage de l'épithélium pavimenteux à l'épithélium cylindrique et où débouchent les glandes du col. Dans ces épithéliomas, on retrouve à la fois, mais avec un degré de prédominance variable, certains caractères d'évolution épidermoïde et d'autres de sécrétion de mucus.

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OBS. 12° XIV A 574.—47 ans. Stade 4. *Épithélioma pavimenteux*. Traitement le 12 décembre 1925 (Ra interne ÷ RX). Guérison apparente pendant 3 ans. En janvier 1928, développement de tumeurs abdominales, une lombaire prévertébrale et une dans la fosse iliaque droite. Mort le 15 mars 1929.

OBS. 13° XIV A 660.—63 ans. Stade 2. *Épithélioma de transition*. Traitement le 23 octobre 1926 (Ra interne). En juillet 1927, signes de métastase hépatique. Persistance de la guérison locale. Mort en septembre 1927.

OBS. 14° XIV A 765.—48 ans. Stade 2. *Épithélioma de transition*. Traitement le 18 octobre 1927 (Ra interne ÷ Ra externe). Guérison apparente pendant un an et demi. En juillet 1929, douleurs abdominales; en août, apparition d'une petite tumeur métastatique dans la paroi abdominale, qui est extirpée chirurgicalement. En octobre 1929, au dernier examen: toux, amaigrissement, sans signes objectifs; persistance de la guérison locale.

OBS. 15° XIV A 774.—53 ans. Stade 2. *Épithélioma pavimenteux épidermoïde*. Traitement le 13 novembre 1927 (Ra interne ÷ Ra externe). Guérison apparente pendant un an et demi. En avril 1929, signes de métastases pulmonaires. Persistance de la guérison locale. Mort le 24 novembre 1929.

OBS. 16° XIV A 783.—46 ans. Stade 3. *Épithélioma pavimenteux épidermoïde*. Traitement le 30 novembre 1927 (Ra interne ÷ Ra externe). En janvier 1928, douleurs intercostales et dans le bras gauche. En avril 1928, la radiographie révèle une métastase dans la tête de l'humérus gauche. En juillet 1928, signes de métastase hépatique. Persistance de la guérison locale. Mort en septembre 1928.

OBS. 17° XIV A 796.—54 ans. Stade 3. *Épithélioma pavimenteux épidermoïde*. Traitement le 9 janvier 1928 (RX ÷ Ra interne). En août 1928, apparition de nodules cutanés multiples, puis signes de généralisation viscérale: amaigrissement, dyspnée, gros foie, ascite. Persistance de la guérison locale. Mort le 5 septembre 1928.

OBS. 18° XIV A 875.—28 ans. Stade 2. *Épithélioma de transition*. Traitement le 9 octobre 1928 (RX ÷ Ra interne). Apparition en août 1929 de douleurs dans le bras gauche. La radiographie met en évidence une métastase de l'extrémité supérieure de l'humérus. Au dernier examen (mars 1930), persistance de la guérison locale.

DISCUSSION DES CAS

A ces observations manque le contrôle de l'autopsie dont la pratique eût certainement, dans la plupart des cas, révélé des localisations insoupçonnées et conduit à des conclusions plus positives quant au mécanisme de la production des métastases. Des données de la seule clinique, il semble toutefois qu'on puisse tirer quelques indications. *Le chemin des métastases*.—La métastase par pénétration directe dans la circulation sanguine existe, à n'en pas douter, en ce qui concerne l'épithélioma du col utérin. Il arrive qu'on rencontre, à l'examen des préparations histologiques, des figures d'envahissement d'un vaisseau incontestablement veineux. Mais elle apparaît très rare par comparaison avec les généralisations par voie lymphatique.

Les observations cliniques conduisent à admettre que, dans le plus grand nombre des cas, le néoplasme s'est propagé par la voie lymphatique. Tantôt les éléments cancéreux, se multipliant dans les ganglions abdominaux, ont déterminé le développement d'une tumeur lombaire ou épigastrique qui a attiré l'attention par des signes de compression. Tantôt ces barrières ganglionnaires ont été rapidement franchies et, alors que la localisation prévertébrale n'était pas encore tangible, survint, comme symptôme apparemment initial, une hypertrophie ganglionnaire sus-claviculaire. C'est le signe de

TROISIÈRE. Cet auteur établit, en 1888, que tout cancer de la cavité abdominale peut se propager à distance aux ganglions sus-claviculaires gauches ; et parmi les observations rapportées par lui figurent plusieurs cas d'épithélioma du col utérin. Il expliquait cet ensemencement rétrograde par la possibilité d'un reflux de la lymphe au niveau de la crosse du canal thoracique, par suite d'une augmentation de pression dans le système veineux. Dans une récente publication ROBERTS admet un tout autre mécanisme de l'envahissement des ganglions sus-claviculaires, axillaires et trachéo-bronchiques dans les cancers abdominaux (prostate et col utérin) : l'obturation néoplasique de la voie lymphatique abdominale entraînerait la dérivation de la lymphe par une voie spinale postérieure, qui serait en communication directe avec les affluents collatéraux du canal thoracique. Quoi qu'il en soit, dans 3 cas, parmi les 18 observations précédentes (4-9-10), le premier signe de certitude de la généralisation a été effectivement une hypertrophie ganglionnaire sus-claviculaire gauche.

Il semble bien que les différentes localisations pulmonaires, osseuses, cérébrales et même hépatiques, représentent des manifestations plus ou moins tapageuses de l'essaimage, par la circulation sanguine, de cellules cancéreuses qui y ont été déversées, après que le processus cancéreux a cheminé lentement et à bas bruit dans l'intérieur du système lymphatique jusqu'à sa terminaison. Peut être aussi arrive-t-il que le crible ganglionnaire laisse passer les éléments néoplasiques sans ralentir leur marche sensiblement : on assiste alors à une généralisation d'emblée, comme cela semble avoir été dans le cas 17.

Délai de production des métastases.—Quel que soit le mécanisme de la dissémination des cellules cancéreuses, on est frappé par la longueur de la période de guérison apparente qui souvent fait suite au traitement et, par conséquent, par la lenteur d'évolution du processus néoplasique (4 ans dans les cas 5 et 6). Sans doute, il peut arriver qu'une tumeur ganglionnaire prévertébrale acquière un très gros volume sans donner de symptômes d'alarme et sans que, chez des femmes grasses, la palpation de l'abdomen permette de révéler leur présence. Mais, on ne peut que formuler des hypothèses sans fondement pour tenter d'expliquer, dans la plupart des cas, la longue quiétude des cellules malignes dans les métastases ganglionnaires alors que, au niveau du col, la progression du cancer semblait avoir subi son cours régulier.

L'examen histologique ne fournit pas d'indication à ce sujet ; on trouve, parmi les cas ayant donné lieu à des métastases, des représentants de toutes les espèces d'épithéliomas habituellement rencontrés au niveau du col ; cependant la proportion des épithéliomas pavimenteux épidermoïdes y dépasse de beaucoup le pourcentage ordinaire.

Contentons-nous donc d'enregistrer le fait clinique (qui n'est d'ailleurs pas particulier au cancer de l'utérus) de la grande inégalité d'évolution et du délai très variable de l'apparition des métastases. Par opposition avec la lenteur de la marche dont nous venons de parler, signalons, en effet, la possibilité d'une très rapide généralisation (cas 17). Il en fut ainsi égale-

ment chez une malade traitée par Ra interne en 1920 (obs. XIV A 193), dont nous avons préféré donner l'histoire résumée à part des précédentes observations. La lésion paraissait limitée au col (stade 1); cependant, au cours d'un examen pratiqué moins d'un mois après le traitement, on percevait déjà une masse abdominale lombaire; 1 mois plus tard, apparaissait un ganglion sus-claviculaire gauche; après 3 mois de plus, une tumeur épigastrique était signalée; enfin des hémoptysies témoignaient du développement de métastases pulmonaires et la malade mourait 14 mois après le traitement.

Mêmes écarts considérables en ce qui concerne la survie des malades. Comparons à ce point de vue la malade de l'observation qui vient d'être rapportée à celles des cas 1, 5 et 6, qui ont survécu plus de 5 ans après leur radiothérapie.

Mais dans aucun cas, une métastase ne s'est démasquée au delà de 4 ans après le traitement, ce qui confirme la correction du délai de 5 années exigé par les conventions pour entériner la validité de la guérison d'un épithélioma du col utérin.

Fréquence des métastases.—On ne peut manquer de remarquer, non sans surprise au premier abord, que les généralisations, rarement observées parmi les malades traitées, dans les premières années, l'ont été ensuite avec une fréquence beaucoup plus grande. L'année 1925 marque à ce point de vue un fâcheux record. Il est à craindre que, parmi les malades traitées en 1926 et surtout en 1927 et 1928, considérées aujourd'hui comme guéries, d'autres cas de métastases se manifestent encore. La constatation d'une telle multiplication pourrait inciter à inculper la radiothérapie de provocation à la métastase! Tout esprit judicieux écarte bientôt une telle supposition.

En réalité, la progression de l'incidence des métastases chez les malades localement guéries a suivi légitimement celle du nombre des malades guéries par les radiations. Ces guérisons sont devenues sans cesse plus fréquentes depuis 1919, grâce aux progrès considérables réalisés en technique radiothérapique. Rappelons, en effet, que la statistique de l'Institut du Radium de Paris, comprenant la totalité des épithéliomas du col traités par les radiations, indique un nombre de guérisons après 5 ans d'observation atteignant: 10 per cent. pour l'année 1919, 17 per cent. pour l'année 1920, 25 per cent. pour 1921, 26 per cent. pour l'année 1922, 30 per cent. pour l'année 1923, 35 per cent. pour 1924; on peut dès maintenant estimer que pour 1925, le nombre des guérisons après 5 ans atteindra 40 per cent.

Au reste, si la fréquence des métastases a augmenté, celles-ci frappent surtout des malades traitées pour des lésions beaucoup plus avancées; dans les premières années, les quelques cas observés concernaient des malades atteintes de cancers au stade 1 ou 2, car la guérison locale des cas plus étendus n'était alors obtenue qu'exceptionnellement. L'accroissement brusque des métastases en 1925 correspond à l'époque où la combinaison systématique de l'irradiation externe transcutanée avec la curiethérapie intracavitaire pour le traitement des malades inopérables a permis de hausser les guérisons de ces cas à un taux jusqu'alors inconnu.

Il semble qu'on puisse expliquer par le même raisonnement pourquoi les cancers ayant donné lieu à des métastases appartenaient pour la plupart (surtout pendant les premières années) à l'espèce épithélioma pavimenteux épidermoïde: ce cancer étant le plus radiosensible des épithéliomas du col fournissait un plus grand nombre de guérisons locales.

CONCLUSIONS

L'étude des récidives extrapelviennes apporte donc une preuve de l'efficacité de la radiothérapie des épithéliomas du col utérin et des progrès réalisés depuis 10 ans dans cette voie. Elle montre que si par l'irradiation correcte du bassin, on peut obtenir la stérilisation d'un cancer propagé à toute la cavité pelvienne, lesensemencements extra-pelviens, préexistant au traitement, échappent évidemment à cette stérilisation. Les ganglions lombaires représentent le centre habituel de ces ensemencements d'où partiront ultérieurement, après une période de latence plus ou moins longue, les cellules génératrices des métastases. Comme la radiothérapie reste impuissante contre les cancers généralisés (l'irradiation des foyers métastatiques essayée plusieurs fois, bien que cela n'ait pas été rapporté dans les résumés ci-dessus, n'a pas empêché la terminaison fatale), il importe d'essayer de prévenir la généralisation. Pour cela, on cherchera à comprendre la région des ganglions lombaires dans le champ des irradiations chaque fois où l'extension des lésions pelviennes fera suspecter leur intégrité.

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HOW FAR CAN RADIUM REPLACE RADICAL SURGERY FOR CANCER OF THE RECTUM

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IN THE treatment of cancer of the rectum radium has been employed for many years, chiefly as a palliative measure, and mainly by intrarectal application in cases regarded as unsuitable for radical surgery. It is only within the last six years that attempts have been made to use radium by interstitial needling in association with the surgery of access with a view to eradication of the disease. Great credit is due to Neumann, of Brussels, for his pioneer work in this direction. Most of the work done has been focused on cases regarded as inoperable or unsuitable for operation.

It is generally recognized that radical surgery for cancer of the rectum *in the early stage* cures a very high percentage of those who recover from the operation but it involves the stigma of colostomy.

It is accepted, in certain histological grades of cancer of the tongue, that radium can be relied on to produce as good, if not better, results (*quâ* the tongue) than mutilation by excision. The author has, in a limited number of cases, more especially when operation has been refused or considered undesirable on general grounds, attempted to find out if adenocarcinoma of the rectum can be placed on the same footing, and whether and under what circumstances it is justifiable to recommend radium in preference to radical excision and colostomy.

It is not proposed in this paper to discuss the value of radium treatment in those cases which have advanced so far that radical surgery is out of the question. Experience shows that much can be done for these and that a few can be relieved of all evidence of disease. The subject has been fully discussed by the author elsewhere.*

It is proposed to consider here how far the use of radium is justifiable in preference to radical surgery. The problem is not only one of radiation *versus* colostomy and excision of the rectum but also radiation *versus* local resection without colostomy.

For many years partial resection of the rectum for an operable growth has been regarded as unsound surgery and has been replaced by some form of radical excision which is usually combined with colostomy.

The recent work of Dr. Cuthbert Dukes,† which, though subject to confirmation in a larger series of cases, shows on histological evidence that

* Radium Treatment of Cancer of the Rectum. *Acta Radiologica*, vol. x, Fasc. 4, No. 56; The Treatment of Carcinoma of the Rectum with Radium. *British Journal of Surgery*, vol. xvii, No. 68.

† *British Journal of Surgery*, vol. xvii, No. 68, 1930.

lymphatic invasion does not occur until the growth has penetrated through the longitudinal muscular coat of the bowel. These observations, based on a very complete histological examination of a hundred consecutive specimens of excised rectums, indicate that surgeons may in future be content with limited resections without permanent colostomy for the early mobile growth which has not commenced to ulcerate. In some instances ulceration occurs early, before the growth has involved by lateral spread the major portion of the circumference. Ulceration indicates downward spread and early penetration of the muscular coat, so that the actual size of the growth, if considered apart from its mobility, is not a sure test of suitability for local resection. The only clinical tests available are a small growth which has free mobility and shows absence of ulceration. The last three cases of this type have been dealt with by local resection; two with temporary colostomy, and one without. All three have been shown subsequently to belong to Class B. It should be mentioned that Class A are those very early cases which have

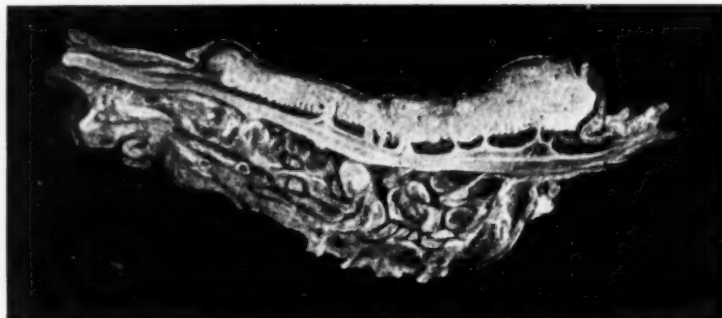


FIG. 1.—Carcinoma of the rectum, early C case. Longitudinal slice of the wall of the rectum, showing the manner in which a malignant growth invades the muscle coat by means of roots which push their way between the segments of the circular muscle.

not invaded the muscular coat, Class B, those which have invaded the muscular coat but not penetrated through it, and Class C, those which have penetrated the muscular coat and invaded the perirectal tissues. (Fig. 1.)

Time alone will show whether this procedure based on histological evidence is justified by ultimate results, though it may be mentioned here that the results of Harrison Cripps over twenty years ago, and Grey Turner in recent years, show that end-results of operations less radical than now considered necessary are remarkably good.

Can radium treatment compete with a local resection which aims at avoiding a permanent colostomy?

These three cases could have been dealt with quite easily and thoroughly by interstitial radiation. Two of them were amenable to vaginal radiation, and the other to a posterior barrage after resection of the coccyx. That these were not so treated, in spite of some successes in similar cases, is due to the fact that it was impossible to give any promise that radium would be

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successful in completely destroying the growth and, if successful, that a recurrence was unlikely.

Sufficient evidence has been obtained to show that an early growth of the rectum can be destroyed with radium without colostomy (or with a temporary colostomy) and without interference with the function of the rectum, though no observations are available, on a five-year basis, as regards recurrence. If, however, local resection with little or no immediate mortality, carried out without permanent colostomy, should replace radical excision for similar cases it would be difficult to advocate radium in preference, because experience shows that adenocarcinomas vary considerably in radioresistance

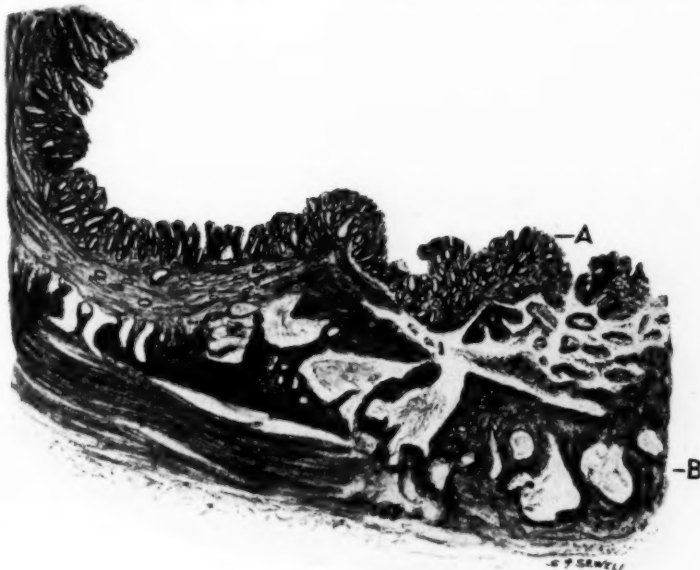


FIG. 2.—The section shows several collections of malignant cells in the submucosa and muscles, but the surface of the ulcer is covered with a thin layer of granulation tissue incorporating some healthy glands. The appearances are unknown in untreated cases, and indicate an attempt at healing and regeneration of the surface epithelium. A.—Regenerated epithelium. B.—Areas of mucoid degeneration.

and in their response to radiation, and so, unfortunately, the result which may be anticipated with radium in any given case cannot be predicted.

All growths of the rectum are regarded as operable, in the absence of metastasis in the peritonæum or liver, provided that the rectum can be removed with the surrounding tissues and all invaded lymphatics clear of the growth, and provided that the rectum is not fixed to bladder, sacrum, or pelvic wall by malignant infiltration. So that an A, or B, and many of the C cases belong to this class. As the growth extends from an early C to a late C so the suitability for radical operation diminishes. Somewhere between these two is the borderline case which is submitted or not to radical operation according to the age and general condition of the patient.

Though in most instances a good case cannot be made out for radium in

the early case in preference to modified radical surgery, there is much more to be said for it as the case approaches the borderline where a radical cure from radical surgery becomes more uncertain and the operative risks increase.

It is not possible to make any statistical comparison as to results in this class but when in doubt as to the wisdom of attempting a radical cure with surgery the surgeon is fully justified in employing radium, provided that he adequately radiates the entire growth and the lines of lymphatic spread in a uniform manner.

The ultimate result, as regards function of the rectum after radiation of

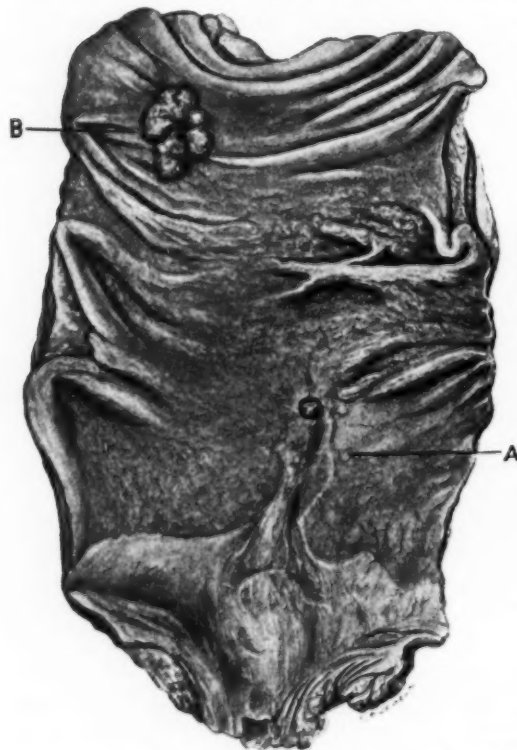


FIG. 3.—Results of radiation. Rectum excised for carcinoma shown at B. At B there is a puckered scar resulting from radiation of a carcinoma nearly three months before the second growth was discovered. No carcinoma could be discovered on section of tissues behind the scar. The small nodule at the upper end of the scar was quite soft. The growth treated was about 1½ inches in diameter. (Mr. Gabriel's case.)

a growth, varies according to the degree of fibrosis which results and whether or not a fibrous stricture follows. The smaller the growth dealt with, the better the prognosis as regards stenosis. Small growths can be destroyed with little or no deformity of the lumen. The degree of fibrosis depends also on variations in reaction. An overdose may cause necrosis and excessive fibrosis with resultant stricture, but a correct dose may secure a perfect result. New epithelium grows over the radiated area (Fig. 408) and it may be difficult to recognize any abnormality of the lumen on digital examination beyond a slight projecting ridge (*Vide* Fig. 3).

Alteration in the size of the lumen of the rectum results from local resections and fibrous strictures are very liable to follow, unless great care is exercised in avoiding sepsis during

healing, and unless any tendency to stricture is checked by careful dilatation during convalescence.

When the operative risks of radical excision as distinct from local resection are considered, especially in cases where the risks are above the average, the arguments in favor of radium are more worthy of consideration.

If, in the future, adenocarcinoma can be graded like squamous-celled carcinoma of the tongue into radiosensitive and radioresistant, the arguments in favor of radium in selected cases may be enhanced. Hitherto, attempts,

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prior to treatment, after removal of a small portion of growth, to differentiate and classify a case histologically have not been fruitful.

Furthermore, if research should reveal some method of sensitization which can be relied on, there will be a wider field for the use of radium in preference to surgery.

At the present time the number of cases dealt with in this class does not justify a too dogmatic opinion. The result in any given case depends on the delivery of an optimum dose, which is dependent on the correct amount of radium, the correct distribution, the correct filtration, and correct time of exposure.

Several unexpected failures have been encountered in the radiation of early growths. Fortunately, in most instances, these failures can and have been made good by radical surgery, but unless it can be shown that pre-operative radiation increases immunity against recurrence patients so treated may have cause for complaint.

Until a much larger series of early cases comes under review it is reasonable to assume that unexpected failures (such as two apparently similar growths treated on supposed identical lines, responding in one case well, in the other badly) may be explained in part by some error in technic and not entirely by variation in radioresistance.

The Treatment of an Operable Growth with Radium.—A small operable growth in the rectum below the peritoneal reflection and clear of the anal canal can, if it involves the anterior or lateral wall in the female, be attacked with needles through the vagina without surgical exposure. In the male the best approach is from behind after removal of the coccyx when the rectum can be mobilized so that the growth becomes accessible whether posterior, lateral or anterior. The same approach is employed for the female if the growth is posterior. If the growth, though small, has commenced to ulcerate, there is a risk of lymphatic spread, and whether the posterior or vaginal route is employed the retrorectal space should be radiated.

If a very small growth (not larger than a penny) is encountered and found to be malignant, and the mobility of the growth is such that it can be freely mobilized from the muscular wall (*i.e.*, an A case) it may be treated with some confidence by the introduction of intrarectal filtered radon seeds without surgical exposure and without glandular attack, though the fact that must not be lost sight of that local resection without colostomy offers in all probability a more certain cure, if the results of Doctor Dukes' investigations are not subject to error.

During the past five years, the author has dealt with over a hundred cases of cancer of the rectum with radium, and lest it should be supposed that radium has been preferred to surgery when surgery is indicated it may be mentioned that over sixty cases have been submitted to radical surgery during the same period.

For every case that has been submitted to radical surgery (or radium treatment), more than one has been found on exploration to be suffering

from secondary visceral deposit and submitted to colostomy only. Of the cases treated with radium only twenty-seven have been regarded as suitable for radical surgery. Some of these have refused colostomy or radical surgery; others have been given the choice. Five of these cases so treated have been subsequently dealt with by radical surgery because the radiation has been either incomplete or inefficient, or has been followed by recurrence, and are now well. Six are apparent cures for varying periods from one year to two and one-half years. One died after excision of the rectum following recurrence. One died after excision of the rectum following preliminary abdominal radiation. One remained well for a year and nine months and died following closure of colostomy. The remaining thirteen (including five cases of carcinoma of the anus) are under observation after treatment for less than a year; one of these has received secondary radium treatment, and another is under treatment with deep X-ray therapy following rapid recurrence. Space does not allow a discussion on technic and dosage but it is important to note that one of the disadvantages of radium treatment consists in the length of time (often two months) which these growths take to completely retrogress and disappear in most instances.

While evidence of growth remains there is uncertainty as to the end-result. When all visible growth has gone a varying amount of fibrosis remains. Uncertainty as to whether any growth remains in the interstices of these fibrous nodules cannot be avoided.

Further, when operative exposure from behind has been the method employed, the wound usually takes as long to heal or longer than after a radical excision. A long operative convalescence can be endured patiently if the prospect of cure is assured, but not so if the prospect remains throughout an uncertain one.

For the very early accessible growth there is much to be said for vaginal or intrarectal (or perirectal) radiation without surgical exposure. If this fails, surgery can follow without delay. Healing is not inhibited after radiation provided that the interval between radiation and operation is not long enough to allow marked fibrosis and diminution of blood supply.

It will be noted from this brief summary that it is too early to report definitely on the results of radium treatment for the operable case.

Nevertheless results show that even when a growth has not penetrated through the bowel wall and is small enough to be accessible to uniform interstitial radiation by one method or another, radium may fail, possibly not always due to want of sensitivity to radium but to imperfect technic. Some of these radium failures have been relieved by radical surgery after a prolonged period of treatment. Even in those cases which remain well without colostomies and with apparently healthy rectums the question of future recurrence is still *sub judice* and on a less secure foundation probably than after resection.

The cases which have so far been considered are those cases of early carcinoma which are situated below the peritoneal reflection and are easily

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accessible to interstitial radiation on the one hand or to local excision on the other.

Two other classes of operable growths remain for consideration:

(1) Those which are above the peritoneal reflection and must, if treated surgically, be submitted either to perineal or abdominoperineal excision with colostomy, or if treated with radium cannot be satisfactorily dealt with except by transperitoneal attack.

(2) Operable cases of squamous-celled carcinoma of the anus.

(1) During the past three years the author has employed radium (both needles and seeds) by the transperitoneal route. (*Vide Fig. 4, British Journal of Surgery.*)

(a) To barrage the upward line of lymphatic spread along the inferior mesenteric vessels as a preliminary to radical excision (at the time of colostomy).

(b) To attack the fixed, inoperable growth which is situated above the peritoneal reflection, or to deal with the upper part of a growth which lies partly above and partly below the peritonæum.

(c) To attack an operable growth above the peritonæum in a patient who is considered too old or too unfit to stand an abdominoperineal excision.

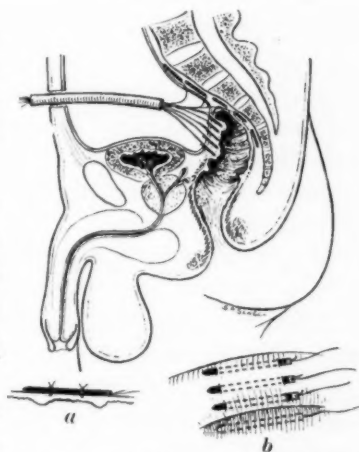


FIG. 4.—Abdominal radiation with needles; a and b, alternative methods of using needles within the abdomen.

Transperitoneal radiation is a far more risky proceeding than perineal radiation. Radium causes a variable amount of inflammation of the peritonæum, often with effusion of fluid in the area attacked, and if this area is not protected from the small gut and drained, there is a risk of paralytic ileus. Further, if the lumen of the bowel is penetrated by a needle and a track is established between the lumen and the peritoneal cavity as the result of radium necrosis, there is considerable risk of general peritonitis.

Experience has shown that the use of radon seeds within the abdomen causes far less disturbance to the peritonæum than radium needles, and is a much safer proceeding, but so far the end-results have not been so encouraging. In the author's experience this observation applies to most other regions treated with radon.

The radon seeds can be left *in situ* and have not so far caused any harm. The removal of the needles often calls for a second anæsthetic.

In only eight cases has radium been employed within the abdomen for a growth above the peritoneal reflection which might have been excised.* In

* Three of these were labeled as "borderline" and have not been included in the twenty-seven operable cases treated with radium. For the purposes of this paper the total should read as thirty.

one of these, seeds were inserted when there were no facilities for radical operation. Subsequently, in another place, excision of the rectum was performed, and the patient died from recurrent hæmorrhage (case already referred to). A microscopic section of the growth after removal is shown (Fig. 2†) and it is most instructive to note that five weeks after radiation new epithelium has commenced to grow over a granulating area and that most of the underlying growth has undergone mucoid degeneration with here and there a few islands of carcinomatous cells. It seems possible that, if operation had been delayed, the growth might have been destroyed with radon and the operation not required.

The other seven cases have all done well but it is not possible to say that any one of them is cured. In each instance, if operation had been carried out, an abdomino perineal excision would have been necessary and was decided against on general grounds.

A number of cases have been treated by transperitoneal radiation under heading (b), which does not come under discussion in this paper, but it may be mentioned that one of these is an apparent cure (two and one-half years) and has no colostomy.

(2) Squamous-celled carcinoma of the anus stands on a somewhat different footing from adenocarcinoma of the rectum.

Early cases, which have not infiltrated deeply into the ischio-rectal fossa, surrounded the anus or invaded the inguinal glands can, I think, be promised an immediate cure with interstitial radiation, combined in some instances with surface radiation. The question of permanent cure cannot yet be answered. So far results in these cases have been excellent with one exception, the case already referred to, in which recurrence followed an apparent cure. This was the first case of the kind treated (1925). Recurrence occurred wide of the original growth and it is probable that the periphery of the growth was inadequately radiated.

There are distinct advantages in the use of radium in these cases over surgical excision.

Radical removal of an anal growth involves removal of the sphincters and a colostomy, whereas with radium in most early cases complete restoration of rectal function can be secured and a colostomy avoided.

CONCLUSION

It is common knowledge that in young people (under thirty years of age) carcinoma of the rectum grows rapidly, gives rise to early metastasis, and usually recurs after radical excision. I have notes of eleven patients under thirty years of age whose rectums I have excised. Not one of these survived three years.

So far as inoperable growths are concerned, the best results which have been secured with radium have been in patients under forty. The same holds good though not to so marked an extent with the operable case.

I have not much evidence to support my view, but I am inclined to think

† Fig. 408 in *British Journal of Surgery*, Vol. xvii, 1930.

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that though there is little hope for a patient under thirty afflicted with carcinoma of the rectum, however treated, he has more chance of a cure with radium than with surgery. The more active the growth the more radio-sensitive it is.

When dealing with cases of adenocarcinoma of the rectum below the peritonæum, except in the very young, it is impossible not to conclude that with the experience available at present the results which may be anticipated are too uncertain to justify preference for radium to surgery unless surgery is refused or contraindicated on some general grounds or the growth is on the borderline between operable and inoperable.

The operative risks of dealing with high growths of the rectum by the abdominoperineal route are considerable so that unless the case is considered to be an exceptionally good operative risk and the growth is sufficiently early to give promise of freedom from recurrence, the employment of radium can be justified. In such cases colostomy may sometimes be avoided with radium treatment, but never with operative treatment.

In cases of squamous-celled carcinoma in the early stage there are strong arguments in favor of the use of radium in preference to surgery. If this fails, colostomy and excision still may be employed in the majority of cases as a radical measure.

It need hardly be added that increased knowledge of the action of radium and greater experience in technic may improve results vastly and modify our views as to its utility in relation to surgery.

At the present time incomplete knowledge and limited experience of the action and use of radium have to be balanced against a standard of surgery which seems to have reached its zenith.

At present radium is like a wild horse which must first be tamed, before it can be harnessed to the surgeon's team. Whether it will take a place as leader, or wheeler, or as a spare, remains to be seen.

FAR-REACHING EFFECTS OF GAMMA RAYS AND SHORT X-RAYS UPON THE HUMAN HEART

ELECTROCARDIOGRAPHIC RESULTS OF CANCER TREATMENTS
GIVEN WITHOUT DIRECT IRRADIATION OF THE HEART

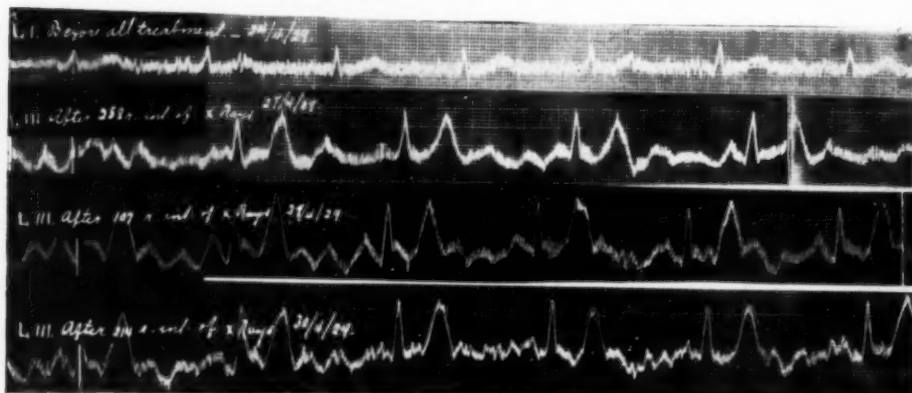
By J. E. GENDREAU, M.D.

OF MONTREAL, CANADA

FROM THE RADIUM INSTITUTE OF MONTREAL

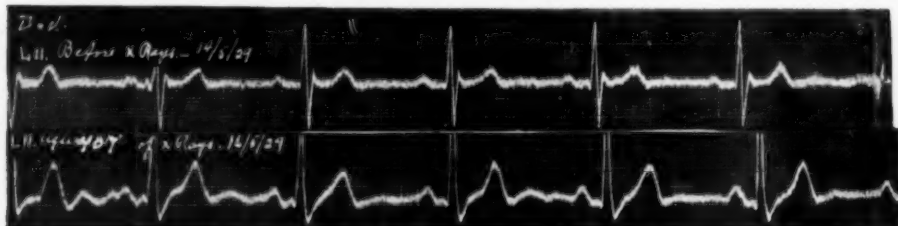
CARDIOVASCULAR disturbances produced by large doses of gamma rays and short X-rays, even when the heart itself has not been directly treated, are accompanied by symptoms which are well known clinically: dyspnoea, tachycardia, general fall of blood-pressure, and asystolia in very serious cases (Coutard et Lavedan; Lavedan et Monod).

As electrocardiograms are helpful in the appreciation of these symptoms, and in the direction of the treatments, we have added systematically the electrocardiographic studies to our clinical examinations, before, during and after the treatments by radium and X-rays.



CASE Ia.—Male, seventy years. Sarcoma of the left leg. Treated by large doses of X-rays—5350 international r. distributed over four fields, in four series of treatments, during twenty-five hours of actual irradiation.

First Series.—Intensive treatment, twenty-eight sittings of thirty minutes each—2996 int. r. in seven days. The records show a marked reaction upon the heart: slower rhythm, higher *Q R S* voltage, high amplitude and long duration of *T*—auricular flutter—diphase and multiplied *P* waves. The tracing presenting such irregularities, a complete rest is ordered for fifteen days.



CASE Ib.—Second Series.—The records of the three leads before treatment are more normal. The rhythm is still slower than before the treatments, but the voltage is higher, *S* deeper. After the treatment of two hours of X-rays, three sittings, 407 int. r., the same effect is obtained as in the first series, but with less intensity.

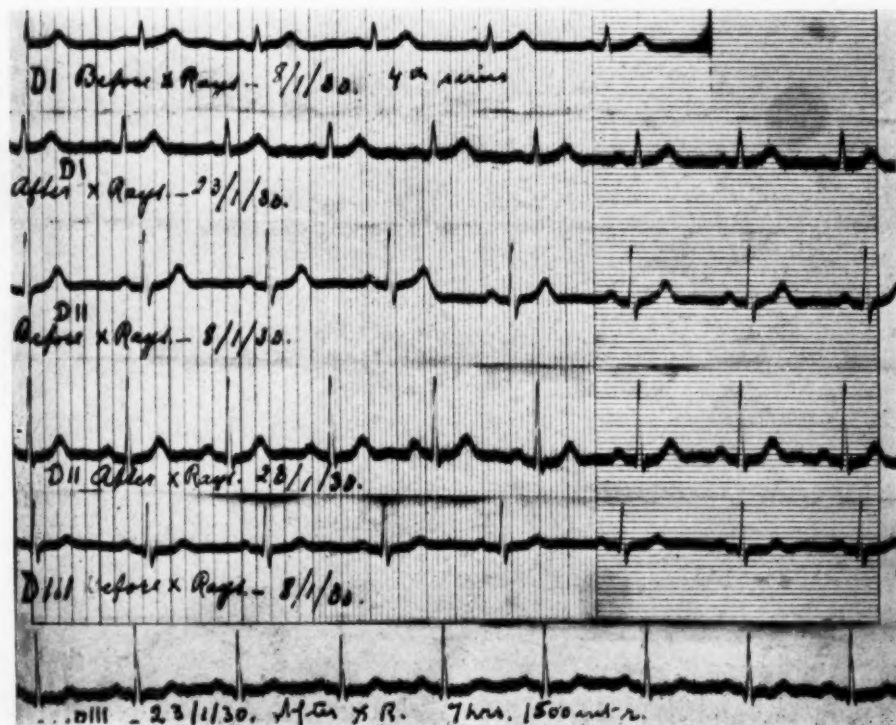
EFFECTS OF RÖNTGEN-RAYS ON HEART

We have many records taken in cancer cases when the irradiation area was outside the region of the heart, which, moreover, was sufficiently protected against external secondary radiation.

Different types of cancers were chosen, of different malignancy, localized, or with metastases, at their onset or well advanced, in different patients, male and female, from ten years of age to seventy-three, in good or bad general condition. Cancers of variable parts of the body—lip, tongue, cheek, neck, right arm and axilla, right breast, bowels, uterus and leg. Cancers treated by radium alone, or X-rays alone, and by radium and X-rays combined, in massive, or in long-protracted doses.



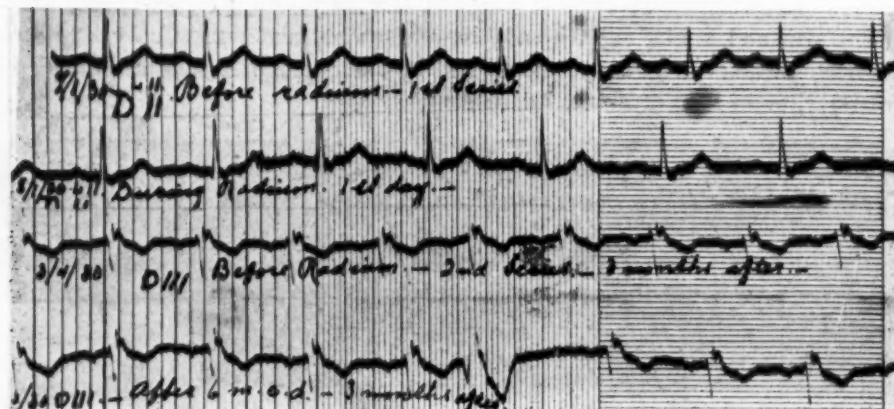
CASE Ic.—A record of the three leads taken a month after the second series: the heart is still fluttering, the T waves are high, and the voltage lower in lead I.



CASE Id.—Fourth Series.—Six months after. Before treatment the heart is in a fair condition. 1500 int. r. are given in fourteen sittings of thirty minutes each distributed over fifteen days. The reaction is evident but mild; the voltage is increased in the three leads, the rhythm is quicker, and the tracings show fine undulations after treatment. It follows that the reaction upon the heart can be mitigated by cautious treatment when the intensive dosage is not imposed by the evolution and nature of the tumor.

J. E. GENDREAU

Technic.—(1) *Gamma Rays or Curitherapy.*—The methods of l'Institut du Radium de Paris were generally applied. Radium sulphate and radon were used in surface applications, and interstitially in needles. Filtration: 0.5 millimetre to 1.5 millimetres of platinum, or 2 millimetres of lead in surface applications, with aluminum, felt and Columbia paste. Distances to the skin: from 1 to 6 centimetres. Moderate prolonged doses. Measuring instruments: electroscopes and Mallet's ionomicrometer with water phantoms.



CASE IIa.—Woman, sixty-three years. Cancer of the left cheek recurring, treated with radium, 11 m.c.d. in fifty-nine hours, in two series of applications.

Leads II.—Before and during radium, on the first day of the first series. The record after treatment shows a slower and irregular rhythm, fine auricular fibrillations with flattening of the P waves, notchings of the ascending branch of T.

Leads III.—In the second series, three months later, show after radium a slower and irregular rhythm, a premature ventricular contraction, with deformity of the QRS complex—the decrease of Q persisting after the compensatory pause. Deeper inverted T. Serrated inverted P wave.



CASE IIb.—X-ray Treatment.—The records before treatment in the three leads, showing a better state of the heart, heavier X-ray doses are given, 200 int. r., in one sitting. The effect is immediate upon the tracings in the three leads taken just after treatment: slower rhythm, lower voltage, in II and III, deeper S in I and II, flattening of the tracings, more flutter and fibrillations in all the leads.

(2) *X-ray or Röntgen Therapy.*—Apparatus: mechanical rectifiers (Standard, Kellykoet); constant potential generators (Gaiffe-Galot-Pilon). Voltages: from 165 kilovolts to 185 kilovolts measured by sphere gaps, calibrated voltmeters (Abraham-Villard-Carpentier), spectograph. Standard Coolidge tubes (G. E. and Gaiffe-Galot-

EFFECTS OF RÖNTGEN-RAYS ON HEART

Pilon) in the air; the patient being protected by lead cylinder (Wappler), or box (Standard), special large enclosing lead-glass receptacles, (two models from l'Institut du Radium de Paris), all motor ventilated; additional thick lead-rubber sheets. Intensity from 2.5 milliamperes to 3.5 milliamperes. Focal skin distance 50 centimetres. Fields at the skin, from 130 square centimetres to 230 square centimetres. Filters: zinc



CASE IIC.—Eight double tracings before and immediately after X-ray sittings on three different days, showing the same comparative changes in all the leads: slower rhythm after treatment, decrease of the voltage, especially in lead III, additional P waves.

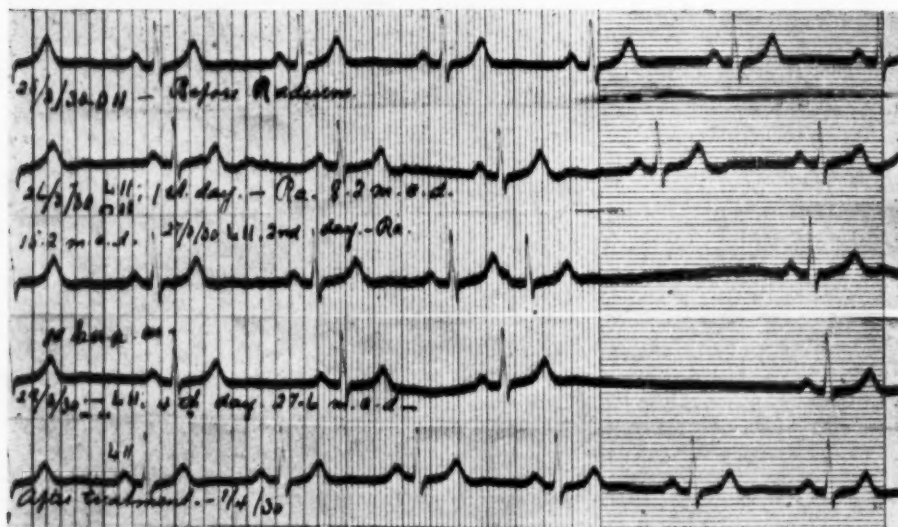
2 millimetres or copper 2 millimetres plus 1 to 3 millimetres aluminum. Percentage of transmission from 42 per cent. to 50 per cent. through 10 centimetres in water phantom (Solomon Beclere). The doses were measured with ionometers (Solomon-Fricke-Glasser) calibrated, and checked with radium, and with the large Kustner's air ionization chamber, from Germany. The small chambers resting on the patients.

These are practical measurements made with ordinary care, but not with the physical laboratory accuracy.

(3) *Electrocardiograms*.—Taken with Boulitte or Victor's G. E. apparatus, with apparently independent electrical sources; but in the tracings the fine heart undulations are often combined with parasitic 60 cycle waves, causing too-frequent notchings.

Dr. L. Jutras assisted in taking out the electrocardiographs.

In each case the changes are appreciated by comparison with the tracings taken *before* treatments. The records show the action of the gamma rays and X-rays upon the heart at a distance; by additional *P* waves, and impure flutter; by flattening of the *P* waves, and auricular fibrillation; by abnormal *Q R S* complexes, in general with lower voltages and reduction of the tracings to a line, occasionally with maximum voltages—very deep *Q* and *S* deflections; by deep inverted *T* waves, sharp and rounded, with occasional notchings in the ascending branch. *RT* is constant but *TP* is generally increased and



CASE IIIa.—Male, fifty-three years. Extensive cancer of the lower lip with gland metastases. 50 m.c.d. of radium in six days.

Leads II.—Five tracings, one before, three during radium, one after. The records during treatment show:

On the first day, slower rhythm, fine undulations, additional *P*, notchings in the ascending branch of *T*—depressions after *T*. On the second day, premature ventricular contractions, *T* being immediately followed by *P*, compensatory pause. On the fourth day, persistence of the arrhythmia—with pauses.

Leads II quickly normal after the cessation of the treatment.

the resulting rhythm slower immediately after a treatment. In premature ventricular contractions on the contrary, *TP* is greatly reduced and *P* immediately follows *T*. The extra systole is generally succeeded by the compensatory pause. Tachycardia is less common than bradycardia.

There is no available space in the article for discussions about the influencing factors of fields, volumes, intensities, time, general condition of the patient, location of cancer, age, difference in after-effects of radium and X-rays, duration of the effects. It is, however, evident that electrocardiograms may be useful in the direction of a cancer treatment by irradiations.